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(54) Tricyclic condensed heterocyclic compounds for the treatment of senile dementic

Tricyclische kondensierte heterocyclische Verbindungen zur Behandlung von seniler Demenz

Composés hétérocycliques condensés tricydiques pour le traitement de la démence sénile

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EP-A- 0 487 071
EP-A- 0 517 221
FR-A- 2 106 515
US-A- 3 716 539

- **CHEMICAL ABSTRACTS, vol. 101, no. 3, 16 July 1984, Columbus, Ohio, US; abstract no. 23414f, P. KUMAR ET AL. 'Phenothiazine derivatives as anti Parkinsonian agents' page 596 ;column 2 ; & INDIAN J. CHEM., SECT. B, vol.22B, no.9, 1983 pages 952 - 954**
- **CHEMICAL ABSTRACTS, vol. 53, no. 22, 25 November 1959, Columbus, Ohio, US; M. BRUNAUD ET AL. 'Adrenolytic activity of various phenothiazine derivatives' column 22521A ; & J. PHYSIOL., vol.49, 1957, PARIS pages 67 - 70**
- **CHEMICAL ABSTRACTS, vol. 116, no. 9, 2 March 1992, Columbus, Ohio, US; abstract no. 83548x, G. GOTO ET AL. 'Preparation of piperidine derivatives containing aminonaphthyl groups as brain function improvers.' page 806 ;column 2 ; & JP-A-03 223 251 (TAKEDA CHEMICAL INDUSTRIES, LTD.) 2 October 1991**

Remarks:
The file contains technical information submitted after the application was filed and not included in this specification

EP 0 607 864 B1

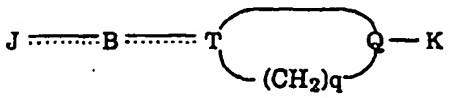
Description

[0001] The present invention relates to a cholinesterase inhibitor, particularly a therapeutic and/or prophylactic agent for senile dementia, Alzheimer's disease, a novel tricyclic condensed benzene compound as an active ingredient thereof, a salt thereof, and a method of production thereof.

[0002] To meet the demand from the aging society, there have been proposed various compounds exhibiting therapeutic and/or prophylactic action against senile dementia, including naturally occurring physostigmine, a cholinesterase inhibitor [e.g., International Journal of Clinical Pharmacology, Therapy and Toxicology, Vol. 29, No. 1, pp. 23-37 (1991)]. However, physostigmine has drawbacks such as short duration of action and strong toxicity.

[0003] On the other hand, synthetic tricyclic condensed ring compounds showing various modes of cholinesterase inhibition have been proposed (US-A-4,895,841 corresponding to JP-A-2(1990)-169569, EP-A-0,441,517 corresponding to JP-A-4(1992)-234845, US-A-(5,106,856).

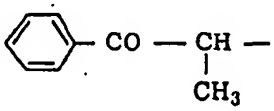
[0004] US-A-4,895,841 discloses a cyclic amine derivative represented by the general formula:



wherein J represents

(a) a substituted or unsubstituted ① phenyl group, ② pyridyl group, ③ pyrazyl group, ④ quinolyl group, ⑤ cyclohexyl group, ⑥ quinoxalyl group or ⑦ furyl group,

(b) a monovalent or divalent group selected from the following groups optionally substituted with a phenyl group; ① indanyl, ② indanonyl, ③ indenyl, ④ indenonyl, ⑤ indandionyl, ⑥ tetralonyl, ⑦ benzosuberonyl, ⑧ indanolyl, ⑨ a group represented by the formula:



(c) a monovalent group derived from a cyclic amide compound,

(d) a lower alkyl group, or

(e) a group represented by the formula R^1-CH=CH- (R^1 represents a hydrogen atom or a lower alkoxycarbonyl group);

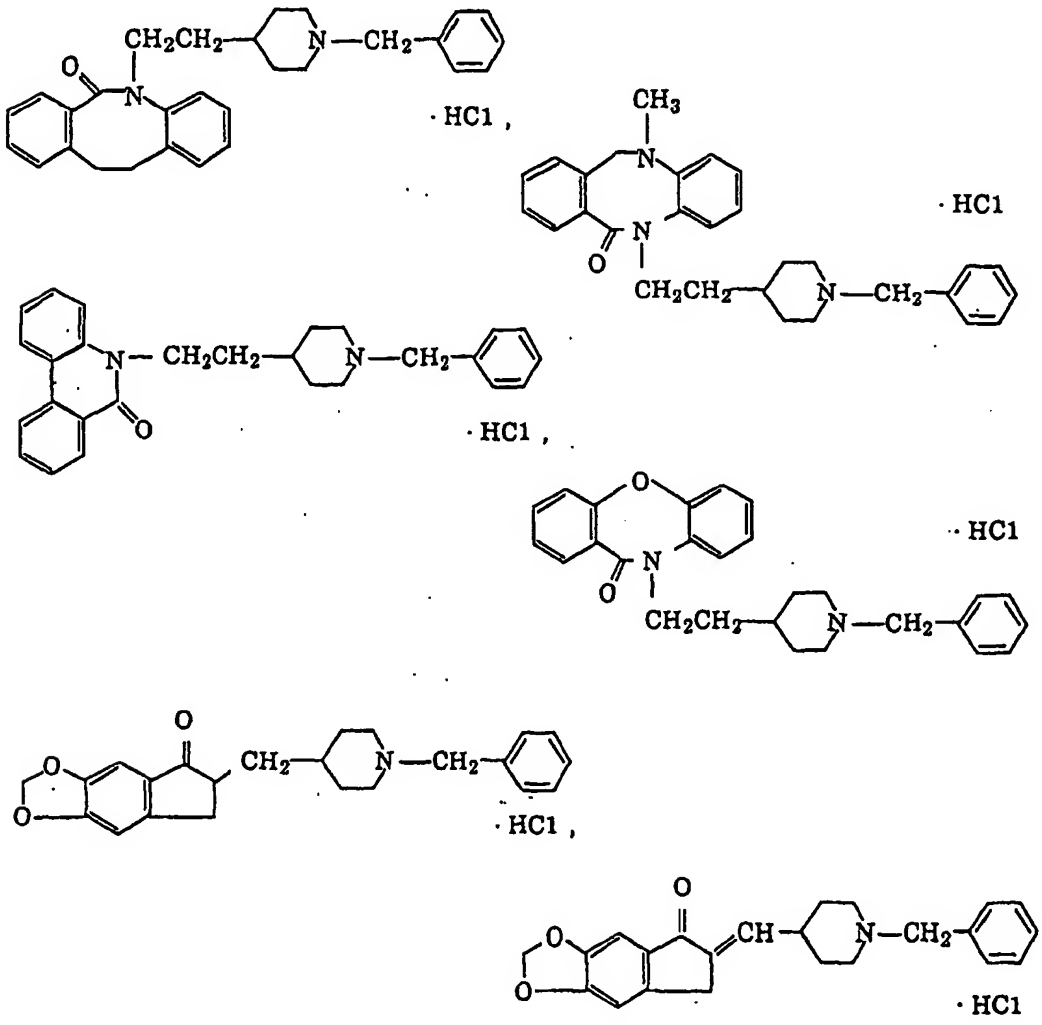
[0005] B represents a group represented by the formula -$(C(R^2)H)_n$-, a group represented by the formula -CO-$(C(R^2)H)_n$-, a group represented by the formula -NR^2-$(C(R^2)H)_n$- (in these formulas, R^2 represents a hydrogen atom, a lower alkyl group, an acyl group, a lower alkylsulfonyl group or an optionally substituted phenyl group or a benzyl group), a group represented by the formula -CO-NR^4-$(C(R^2)H)_n$- in which R^4 represents a hydrogen atom, a lower alkyl group or a phenyl group, a group represented by the formula -CH = CH-$(C(R^2)H)_n$-, a group represented by the formula -O-COO-$(C(R^2)H)_n$-, a group represented by the formula -O-CO-NH-$(C(R^2)H)_n$-, a group represented by the formula -NH-CO-$(C(R^2)H)_n$-, a group represented by the formula -CH2-CO-NH-$(C(R^2)H)_n$-, a group represented by the formula -CO-NH-$(C(R^2)H)_n$-, a group represented by the formula -C(OH)H-$(C(R^2)H)_n$- (in the above formulas, n represents an integer from 0 to 10; R^2 represents a hydrogen atom or a methyl group in such way that the alkylene group represented by the formula -$(C(R^2)H)_n$- has no substituent or has one or more methyl groups), a group represented by the formula =$(CH-CH=CH)_b$- in which b represents an integer from 1 to 3, a group represented by the formula =CH-$(CH_2)_c$- in which c represents an integer from 0 to 9, a group represented by the formula =$(CH-CH)_d$= in which d represents an integer from 0 to 5, a group represented by the formula = CO-CH = CH-CH_2-, a group represented by the formula -CO-CH_2-C(OH)H-CH_2-, a group represented by the formula -C(CH_3)H-CO-NH-CH_2-, a group represented by the formula -CH=CH-CO-NH-$(CH_2)_2$-, a group represented by the formula -NH-, a group represented by the formula -O-, a group represented by the formula -S-, a dialkylaminoalkylcarbonyl group or a lower alkoxycarbonyl group;

T represents an atom of nitrogen or carbon;

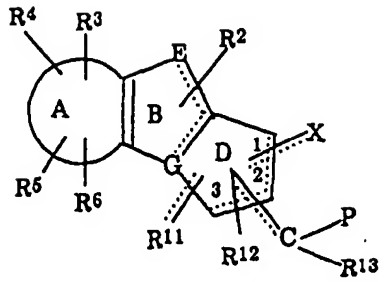
Q represents an atom of nitrogen or carbon or a group represented by the formula

K represents a hydrogen atom, a substituted or unsubstituted phenyl group, an arylalkyl group optionally substituted with phenyl group, a cinnamyl group optionally substituted with phenyl group, a lower alkyl group, a pyridylmethyl group, a cycloalkylalkyl group, an adamantanemethyl group, a furylmethyl group, a cycloalkyl group, a lower alkoxycarbonyl group or an acyl group; q represents an integer from 1 to 3; ..... Represents a single bond or a double bond or a pharmaceutically acceptable salt thereof.

[0006] Specifically, the same publication describes the following tricyclic condensed ring compounds:



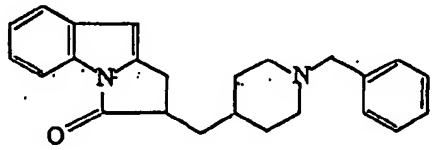
[0007] EP-A-0,441,517 describes a tricyclic amine compound represented by the formula:



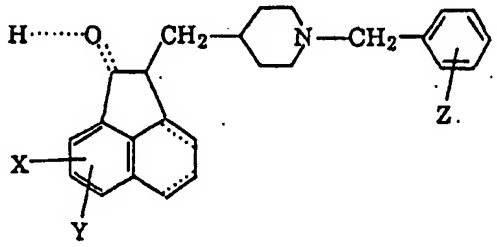
[I]

wherein P represents a group such as an N-substituted piperidino-1-yl-methyl group or an N-substituted piperazino-1-yl-methyl group; G represents carbon or nitrogen; E represents carbon, nitrogen, oxygen or sulfur; ring A is an aromatic ring such as of benzene, pyridine or thiophene, and a pharmaceutical composition containing it as an active ingredient.

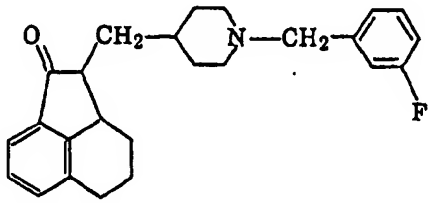
[0008] The same publication describes that a compound of formula [I], having ring system ABD of 1H-pyrrolo[1,2-a] indol-1-one, cyclopento[d]indol-3-one, cyclopento[b](benzo[b]thieno)-1-one, 1H-pyrrolo[1,2-a](6-azaindol)-1-one or pyrrolo[1,2-a](thieno[2,3-b]pyrrol)-1-one, possesses cholinesterase inhibitory activity, and that a pharmaceutical composition containing it as an active ingredient enhances memory in patients with dementia or Alzheimer's disease. Specifically, a compound represented by the following formula, for example, is described.



[0009] US-A-5,106,856 describes a compound represented by the formula:



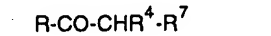
wherein X represents a hydrogen atom, a hydroxyl group, a nitro group, a lower alkyl group or a lower alkoxy group; Y represents a hydrogen atom or a lower alkoxy group; X and Y may bind together to form an OCH_2O group. Specifically, a compound represented by the following formula, for example, is described.



[0010] However, none of US-A-4,895,841, EP-A-0,441,517 and US-A-5,106,856 give no disclosure or suggestion

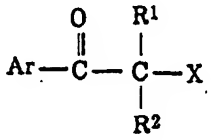
concerning a tricyclic condensed ring compound wherein an N-substituted piperidino-1-yl-methyl or N-substituted piperidino-1-yl-ethyl group, as a substituent, is bound to a benzene ring thereof via a carbonyl group, though they disclose tricyclic condensed ring compounds wherein an N-substituted piperidino-1-yl-methyl or N-substituted piperidino-1-yl-ethyl group is bound directly to the heterocyclic ring or nonaromatic carbon ring thereof.

[0011] Also, US-A-4,285,961 corresponding to JP-A-54(1979)-22333 discloses a compound represented by the formula:

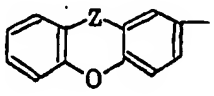


wherein R represents a group such as a 2-dibenzothienyl group: R^4 represents an atom or group such as H; R^7 represents $-(CH_2)_n-Z$ (n represents an integer from 1 to 3; Z represents $-NR^1R^2$ (R^1 and R^2 independently represent H or a C_{1-4} alkyl group, and R^1 and R^2 may bind together to form a C_{4-7} alkylene group or a 3-oxypentamethylene group), as an intermediate for the synthesis of a basic thioether compound possessing antifungal, antibacterial, antiinflammatory and other activities, but gives no disclosure concerning cholinesterase inhibitory action or therapeutic and/or prophylactic drug action against senile dementia.

[0012] EP-A-0,117,233 corresponding to JP-A-59(1984)-167546 describes a compound represented by the formula:



wherein Ar represents a structure such as the following:

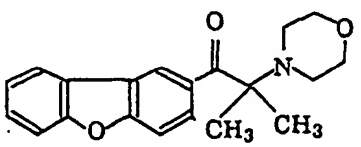


(Z represents a direct bond, a $-CH_2-$ group, a $-CH_2CH_2-$ group or an -O- group); X represents the amino group $-N(R^{11})(R^{12})$ in which R^{11} represents a hydrogen atom, an alkyl group having 1 to 12 carbon atoms, an alkyl group having 2 to 4 carbon atoms substituted with one or more groups selected from the group consisting of the OH, alkoxy groups having 1 to 4 carbon atoms, CN and $-COO-C_{1-4}$ alkyl groups, an alkenyl group having 3 to 5 carbon atoms, a cyclohexyl group, a phenylalkyl group having 7 to 9 carbon atoms, a phenyl group, or a phenyl group substituted with C1, an alkyl group having 1 to 4 carbon atoms, OH, an alkoxy group having 1 to 4 carbon atoms or a $-COO-C_{1-4}$ alkyl group; R^{11} and R^1 may bind together to form a $-CH_2OCH_2-$ group;

R^{12} represents one of the groups specified for R^{11}, or R^{11} and R^{12} may bind together to form an alkylene group having 5 to 7 carbon atoms or an alkylene group having 3 to 7 carbon atoms containing an -O- group, an -S- group or $-N(R^{14})-$; R^{12} and R^2 may bind together to form an alkylene group having 1 to 8 carbon atoms, a phenylalkylene group having 7 to 10 carbon atoms or an oxyalkylene group having 2 to 4 carbon atoms or an azaalkylene group;

R^1 and R^2 independently represent a group such as an alkyl group having 1 to 8 carbon atoms.

[0013] Specifically in this reference, a compound represented by the following formula, for example, is described as a photosetting coloring composition.



[0014] However, that publication gives no disclosure concerning cholinesterase inhibiting action or therapeutic and/

or prophylactic drug action against senile dementia.

[0015] US-A-3716539 and FR-A-2106515 disclose dibenzofuran derivatives which possess hypotensive activity and antiviral activity respectively.

[0016] Chem. Abs. 101(1984), 23414f and Chem. Abs. 53(1959), 22521a disclose phenotiazine derivatives.

[0017] EP-A-0487071 refers to compounds comprising benzo condensed monoheterocyclic compounds which exhibit cholinesterase inhibitory activity.

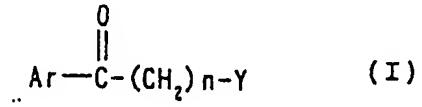
[0018] EP-A-0517221 discloses acenaphthalene derivatives which are useful for alleviating various memory dysfunction characterized by a cholinergic deficit such as Alzheimer's disease.

[0019] To cope with the increasing incidence of senile dementia, there is a need for the development of an excellent therapeutic and/or prophylactic agent for senile dementia which exhibits more potent action for a longer duration with lower toxicity, in comparison with conventional compounds known to possess therapeutic and/or prophylactic activity against senile dementia.

[0020] With this situation in mind, the present inventors investigated the bioactivities and pharmacologic actions of various heterocyclic compounds, including new ones, and stumbled upon the fact that a tricyclic condensed benzene derivative of unique chemical structure, which is characterized by an optionally substituted amino-alkyl or nitrogen-containing saturated heterocyclic-alkyl group being bound to the benzene of the tricyclic condensed benzene ring via a carbonyl group possesses unexpectedly excellent therapeutic and/or prophylactic activity against senile dementia based on its unique chemical structure.

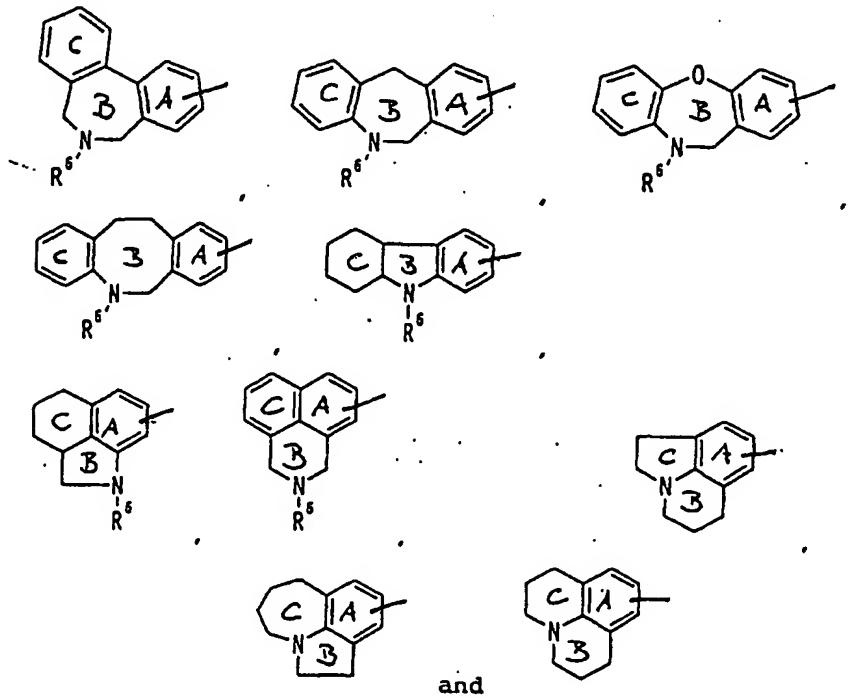
[0021] The present inventors made further investigations based on this finding, and developed the present invention. Accordingly, the present invention relates to:

(1) A compound of the formula:



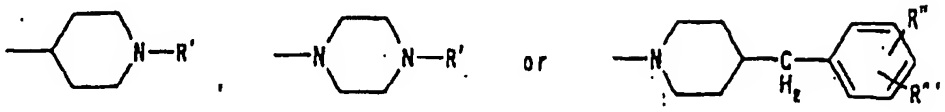
(I)

wherein Ar is selected from the group consisting of the formula:



and

wherein ring A has no substituent, and
wherein ring B or C is optionally subsituted by an oxo and/or C_{1-6} alkyl, and R^6 is hydrogen, C_{1-6} alkyl, formyl, C_{1-6} alkyl-carbonyl, benzoyl or benzyl optionally substituted by C_{1-4} alkoxy;
Y is a group of the formula:



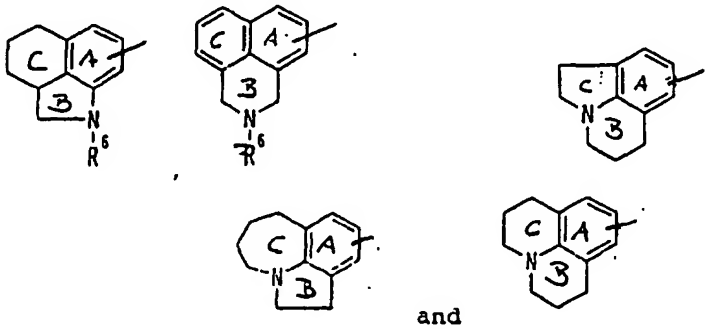
wherein

R' is (1) a benzyl which may be substituted with 1 or 2 substituents selected from the group consisting of C_{1-6} alkyl, halogen, nitro, cyano, amino, mono- or di-C_{1-6} alkylamino, hydroxy, C_{1-6} alkoxy, phenyl-C_{1-4} alkoxy and C_{1-4} alkylenedioxy, (2)cyclohexyl, (3) phenyl, (4) formyl, (5) C_{1-6} alkyl-carbonyl, (6) benzoyl or (7) C_{1-6} alkoxy-carbonyl or (8) hydrogen;
R" and R"' are the same or different and are hydrogen, C_{1-6} alkyl, halogen, nitro, cyano, hydroxy, C_{1-6} alkoxy, phenyl-C_{1-4} alkoxy or C_{1-4} alkylenedioxy;
n is an integer of 2 or 3,

or a salt thereof.

(2) A compound as claimed before , wherein Y is a 4-piperidinyl or 1-piperazinyl group which is optionally substituted by (i) cyclohexyl, (ii) phenyl, (iii) benzyl optionally substituted by 1 or 2 subtituents selected from the group consisting of halogen, C_{1-6} alkyl, C_{1-6} alkoxy, hydroxy, nitro, amino and cyano, (iv) C_{1-6} alkoxy-carbonyl, (v) C_{1-6} alkyl-carbonyl, (vi) benzoyl or (vii) formyl.

(3) A compound as claimed before , wherein Ar is selected from the group consisting of the formula:



and

wherein ring A, ring B, ring C and R^6 have the same definitions as in (1).

(4) A compound according to formula (I), wherein Ar is 1,2,2a,3,4,5-hexahydrobenz[cd]indol-6-yl, 1-formyl-1,2,2a,3,4,5-hexahydrobenz[cd]indol-6-yl, 5,6-dihydro-2(1H)-oxo-4H-pyrrolo[3,2,1-ij]quinolin-8-yl, 4-oxo-1,2,5,6-tetrahydro-4H-pyrrolo[3,2,1-ij]quinolin-8-yl, 1,2,4,5,6,7-hexahydro-2-oxoazepino[3,2,1-hi]indol-9-yl or 2,3,6,7-tetrahydro-5-oxo-1H,5H-benzo[ij]quinolizin-9-yl.

(5) A compound of formula (I), wherein Y is a 1-benzyl-4-piperidinyl, 4-benzyl-1-piperazinyl or 4-benzyl-1-piperidinyl.

(6) A compound of formula (I), which is

8-[3-[4-[(3-methylphenyl)methyl]-1-piperazinyl]-1-oxopropyl]-1,2,5,6-tetrahydro-4H-pyrrolo[3,2,1-ij]quinolin-4-one or a salt thereof,

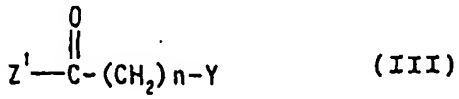
8-[3-[4-[(3-chlorophenyl)methyl]-1-piperazinyl]-1-oxopropyl]-1,2,5,6-tetrahydro-4H-pyrrolo[3,2,1-ij]quinolin-4-one or a salt thereof,
8-[3-[4-[(2-methylphenyl)methyl]-1-piperazinyl]-1-oxopropyl]-5,6-dihydro-4H-pyrrolo[3,2,1-ij]quinolin-2(1H)-one or a salt thereof,
8-[3-[4-[(3-chlorophenyl)methyl]-1-piperazinyl]-1-oxopropyl]-5,6-dihydro-4H-pyrrolo[3,2,1-ij]quinolin-2(1H)-one or a salt thereof,
8-[3-[1-(phenylmethyl)-4-piperidinyl]-1-oxopropyl]-1,2,5,6-tetrahydro-4H-pyrrolo[3,2,1-ij]quinolin-4-one or a salt thereof,
8-[3-[1-[(4-methylphenyl)methyl]-4-piperidinyl]-1-oxopropyl]-1,2,5,6-tetrahydro-4H-pyrrolo[3,2,1-ij]quinolin-4-one or a salt thereof,
8-[3-[1-[(3-methoxyphenyl)methyl]-4-piperidinyl]-1-oxopropyl]-1,2,5,6-tetrahydro-4H-pyrrolo[3,2,1-ij]quinolin-4-one or a salt thereof,
8-[3-[1-[(2,4-dimethylphenyl)methyl]-4-piperidinyl]-1-oxopropyl]-1,2,5,6-tetrahydro-4H-pyrrolo[3,2,1-ij]quinolin-4-one or a salt thereof,
8-[3-[1-[(2,5-dimethylphenyl)methyl)-4-piperidinyl]-1-oxopropyl]-1,2,5,6-tetrahydro-4H-pyrrolo[3,2,1-ij]quinolin-4-one or a salt thereof,
8-[3-[1-[(4-chlorophenyl)methyl]-4-piperidinyl]-1-oxopropyl]-1,2,5,6-tetrahydro-4H-pyrrolo[3,2,1-ij]quinolin-4-one or a salt thereof,
8-[3-[1-[(4-nitrophenyl)methyl]-4-piperidinyl]-1-oxopropyl]-1,2,5,6-tetrahydro-4H-pyrrolo[3,2,1-ij]quinolin-4-one or a salt thereof,
8-[3-[1-[(phenylmethyl)methyl]-4-piperidinyl]-1-oxopropyl]-5,6-dihydro-4H-pyrrolo[3,2,1-ij]quinolin-2(1H)-one or a salt thereof,
8-[3-[1-[(3-methoxyphenyl)methyl)-4-piperidinyl]-1-oxopropyl]-5,6-dihydro-4H-pyrrolo[3,2,1-ij]quinolin-2(1H)-one or a salt thereof,
8-[3-[4-(phenylmethyl)-1-piperidinyl]-1-oxopropyl]-1,2,5,6-tetrahydro-4H-pyrrolo[3,2,1-ij]quinolin-4-one or a salt thereof,
8-[3-[4-(phenylmethyl)-1-piperidinyl]-1-oxopropyl]-5,6-dihydro-4H-pyrrolo[3,2,1-ij]quinolin-2(1H)-one or a salt thereof,
1-(1,2,2a,3,4,5-hexahydrobenz[cd]indol-6-yl)-3-[1-(phenylmethyl)piperidin-4-yl]-1-propanone or a salt thereof,
1-(1-methyl-1,2,2a,3,4,5-hexahydrobenz[cd]indol-6-yl)-3-[1-(phenylmethyl)piperidin-4-yl]-1-propanone or a salt thereof,
1-[2-(phenylmethyl)-2,3-dihydro-1H-benz[de]isoquinolin-6-yl]-3-[1-(phenylmethyl)-4-piperidinyl]-1-propanone or a salt thereof,
8- [3-[1-[(3-fluorophenyl)methyl]-4-piperidinyl]-1-oxopropyl]-1,2,5,6-tetrahydro-4H-pyrrolo[3,2,1-ij]quinolin-4-one or a salt thereof, or
8-[3-[1-[(2-hydroxyphenyl)methyl]-4-piperidinyl]-1-oxopropyl]-1,2,5,6-tetrahydro-4H-pyrrolo[3,2,1-ij]quinolin-4-one or a salt thereof.

(7) A method for producing compounds of formula (1), which comprises

1) reacting a compound of the formula:

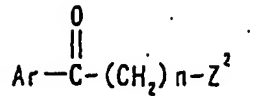
Ar-H (II)

wherein Ar has the same definition as indicated above, or a salt thereof, with a compound of the formula:



(III)

wherein Z^1 is a leaving group and the other symbols have the same definitions as indicated above, or a salt thereof, or
2) reacting a compound of the formula:



(IV)

or a salt thereof, with a compound of the formula:

$$Z^3\text{-}Y \qquad (V)$$

wherein Z^2 and Z^3 are groups capable of reacting with each other to be removed; and the other symbols have the same definitions as indicated above or a salt thereof.

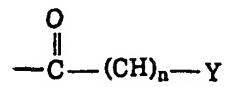
(8) A pharmaceutical composition which contains a compound defined above

(9) Use of a compound as defined above or a pharmaceutically acceptable salt thereof, as a component in the preparation of a cholinesterase inhibitory composition.

(10). A cholinesterase inhibitory composition which contains an effective cholinesterase inhibiting amount of a compound as claimed in claim 1 or a pharmaceutically acceptable salt thereof and a pharmacologically acceptable carrier.

(11) A composition as indicated above, for use in the treatment of senile dementia and/or Alzheimer's disease.

[0022] The compound (I) or salts thereof of the present invention are novel compounds having structural characteristics in that the substituent:



wherein the symbols are as defined above, is bound to a carbon atom of a benzene ring of a tricyclic condensed benzene ring including at least one heterocyclic ring as a component ring, and it. exhibits excellent therapeutic and/or prophylactic actions for senile dementia based on these characteristics.

[0023] With respect to the above formulas, n represents an integer of 2 or 3.

[0024] The tricyclic condensed benzene ring group for Ar has a ring condensation pattern represented by one of the formulas as defined above.

[0025] Rings B and C may be optionally substituted by an oxo and/or $C_{1\text{-}6}$ alkyl (e.g. methyl, ethylchlor, n-propyl, isopropyl, n-butyl, isobutyl, trt-otyl, n-penthyl, n-hexyl).

[0026] R^6 is hydrogen, $C_{1\text{-}6}$ alkyl (e.g. methyl, ethylchlor, n-propyl, isopropyl, n-butyl, isobutyl, trt-otyl, n-penthyl, n-hexyl), formyl, $C_{1\text{-}6}$ alkyl-carbonyl (e.g., methylcarbonyl, ethylcarbonyl, propylcarbonyl), benzoyl benzyl or benzyl optionally substituted by $C_{1\text{-}4}$ alkoxy (e.g., methoxy, ethoxy, propyloxy, buthyloxy, isopropyloxy).

[0027] Y is as defined above.

[0028] The $C_{1\text{-}6}$ alkyl group for R', R" and R"' in the group Y is the same as mentioned above.

[0029] The $C_{1\text{-}6}$ alkoxy group mentioned for R', R" and R"' in the group Y is exemplified by methoxy, ethoxy, propyloxy, buthyloxy, isopropyloxy and this is also valid of the $C_{1\text{-}4}$ alkoxy group in the term phenyl-$C_{1\text{-}4}$ alkoxy.

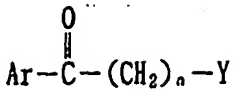
[0030] The mono-or-di- $C_{1\text{-}6}$ alkylamino for R' in the group Y can be exemplified by methylamino, ethylamino, propylamino, dimethylamino, and diethylamino.

[0031] The $C_{1\text{-}6}$ alkyl-carbonyl group represented by R' in the group 4 can be exemplified by methylcarbonyl, ethylcarbonyl, propylcarbonyl.

[0032] The $C_{1\text{-}6}$ alkoxy-carbonyl group represented by R' in the group Y can be exemplified by methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isobutoxycarbonyl.

[0033] More specifically, the following compounds (and salts thereof) categorized under compounds (I) are preferred.

Table 1



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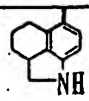
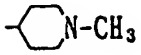
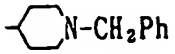
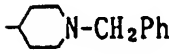
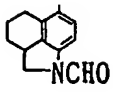
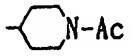
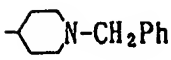
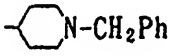
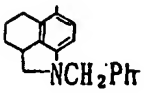
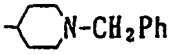
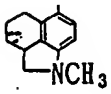
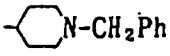
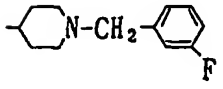
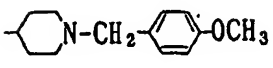
1		2	
2		2	
3		2	
4		3	
5		2	
6		2	
7		2	
8		2	
9		2	
10		2	
11		2	

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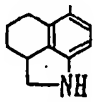
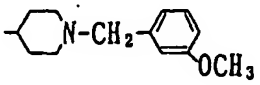
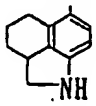
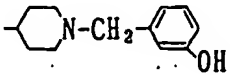
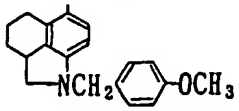
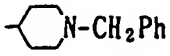
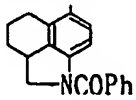
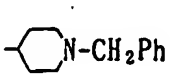
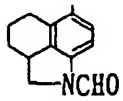
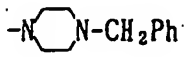
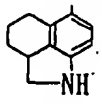
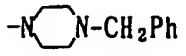
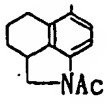
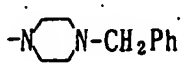
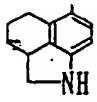
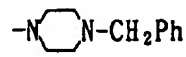
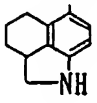
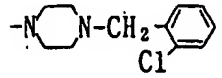
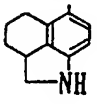
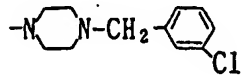
12		2	
13		2	
14		2	
15		2	
16		2	
17		2	
18		2	
19		3	
20		2	
21		2	

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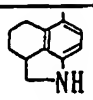
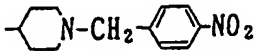
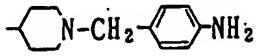
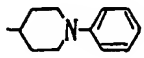
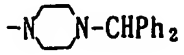
22		2	
23		2	
24		2	
25		2	

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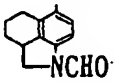
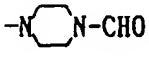
27		2	

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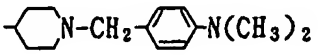
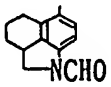
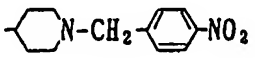
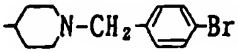
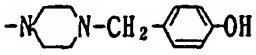
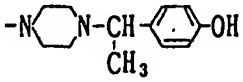
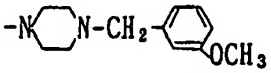
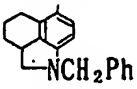
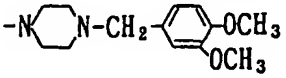
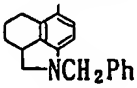
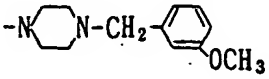
28		2	
29		2	
30		2	
31		2	
32		2	
33		2	
34		2	
35		2	

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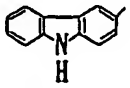
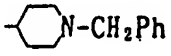
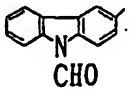
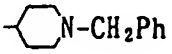
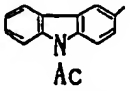
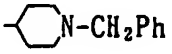
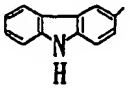
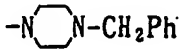
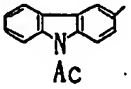
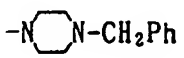
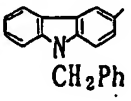
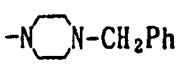
36		2	
37		2	
38		2	
39		2	
40		2	
41		2	

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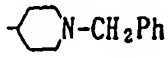
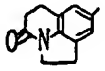
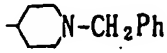
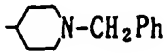
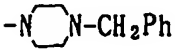
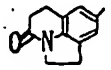
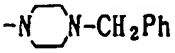
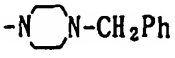
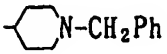
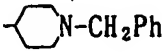
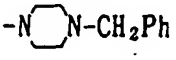
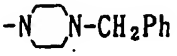
42		2	
43		2	
44		2	
45		2	
46		2	
47		2	
48		2	
49		2	
50		2	
51		2	

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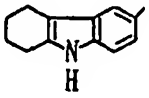
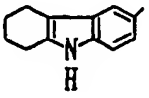
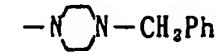
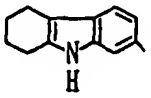
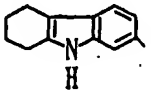
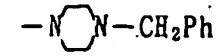
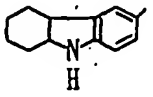
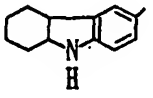
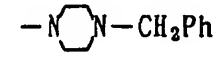
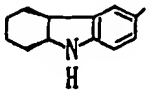
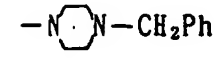
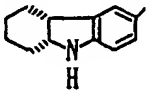
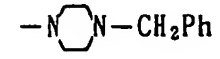
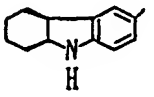
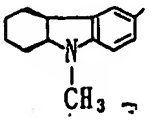
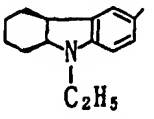
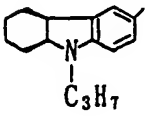
52		2	
53		2	
54		2	
55		2	
56		2	
57		2	
58		2	
59		2	
60		2	
61		2	
62		2	
63		2	

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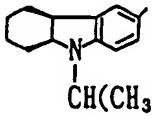
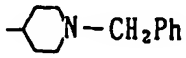
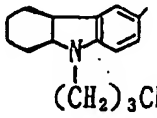
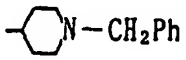
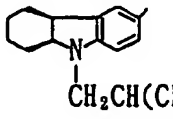
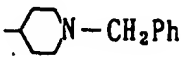
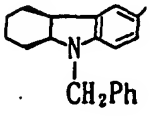
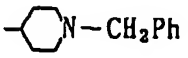
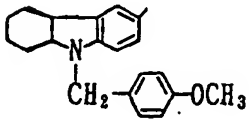
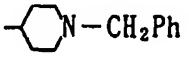
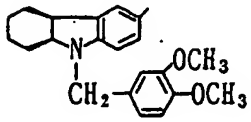
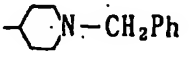
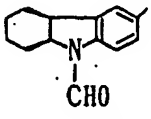
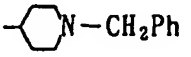
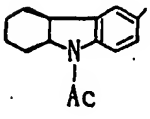
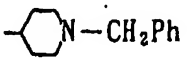
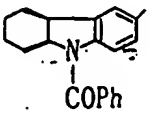
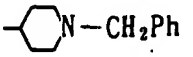
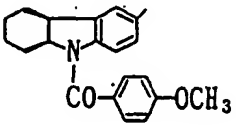
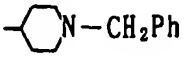
64		2	
65		2	
66		2	
67		2	
68		2	
69		2	
70		2	
71		2	
72		2	
73		2	

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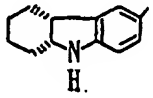
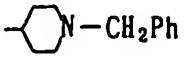
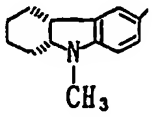
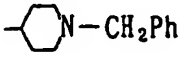
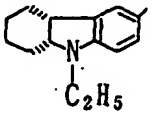
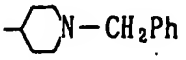
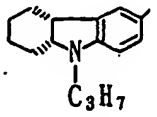
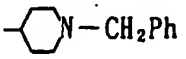
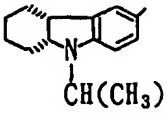
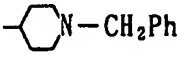
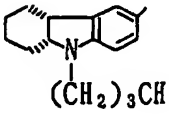
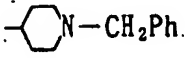
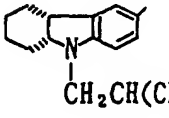
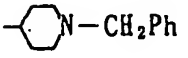
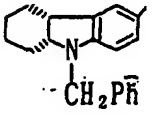
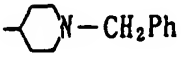
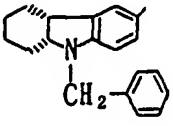
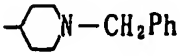
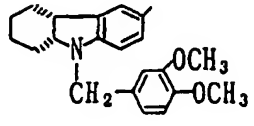
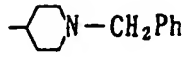
74		2	
75		2	
76		2	
77		2	
78		2	
79		2	
80		2	
81		2	
82		2	
83		2	

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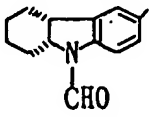
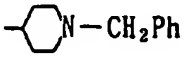
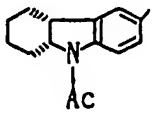
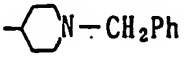
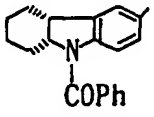
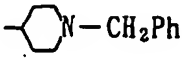
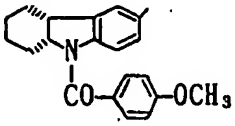
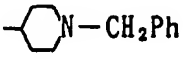
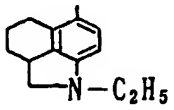
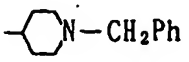
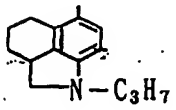
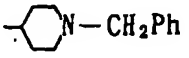
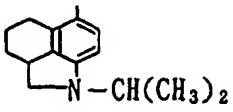
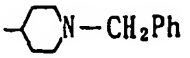
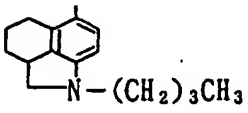
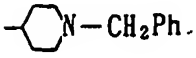
84		2	
85		2	
86		2	
87		2	
88		2	
89		2	
90		2	
91		2	

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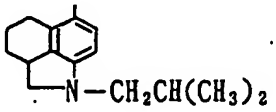
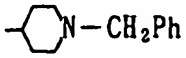
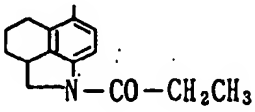
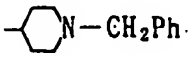
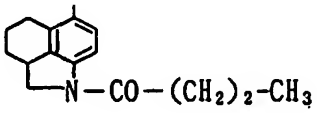
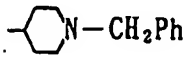
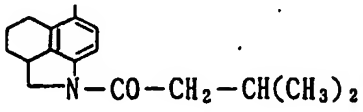
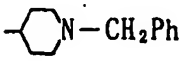
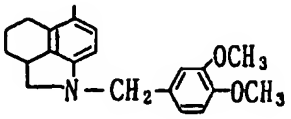
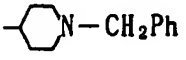
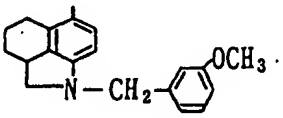
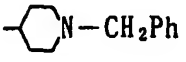
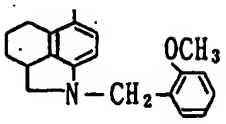
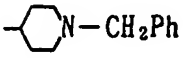
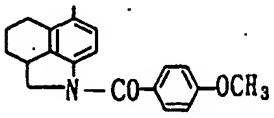
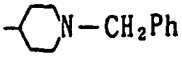
92		2	
93		2	
94		2	
95		2	
96		2	
97		2	
98		2	
99		2	

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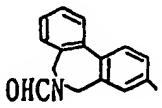
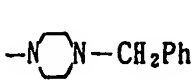
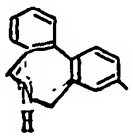
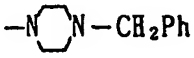
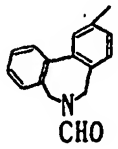
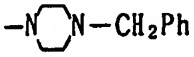
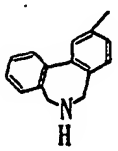
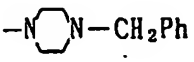
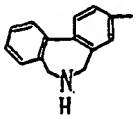
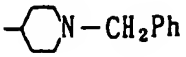
100		2	
102		2	
101		2	
103		2	
104		2	

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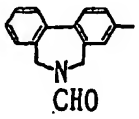
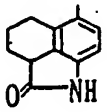
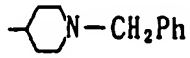
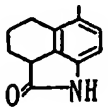
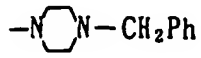
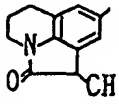
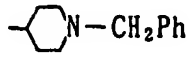
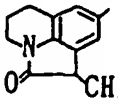
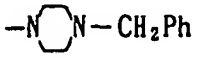
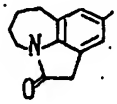
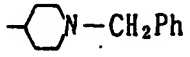
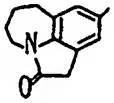
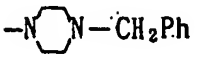
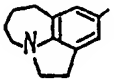
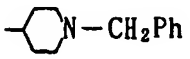
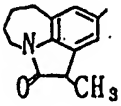
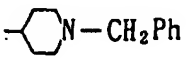
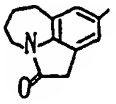
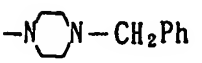
105		2	
106		2	
107		2	
108		2	
109		2	
110		2	
111		2	
112		2	
113		2	
114		2	

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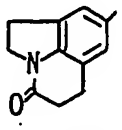
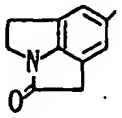
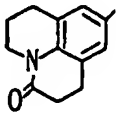
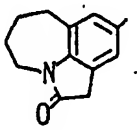
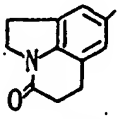
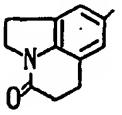
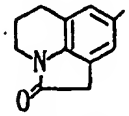
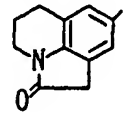
115		2	
116		2	
117		2	
118		2	
119		2	
120		2	
121		2	
122		2	

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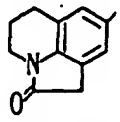
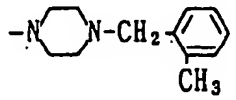
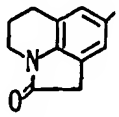
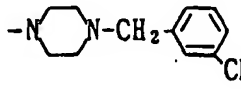
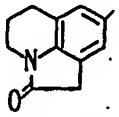
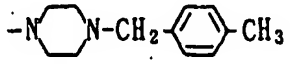
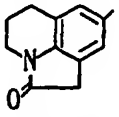
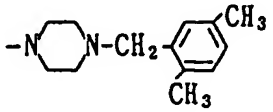
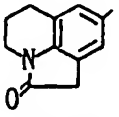
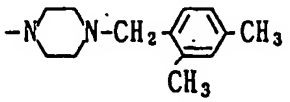
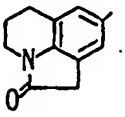
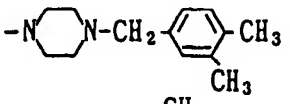
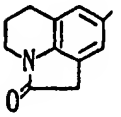
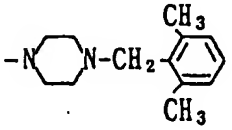
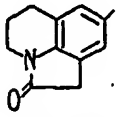
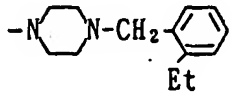
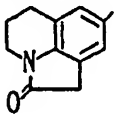
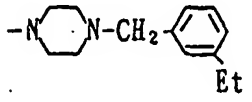
123		2	
124		2	
125		2	
126		2	
127		2	
128		2	
129		2	
130		2	
131		2	

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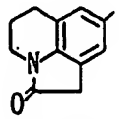
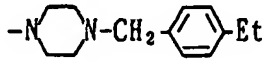
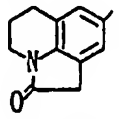
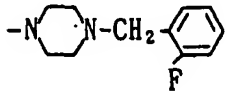
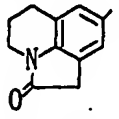
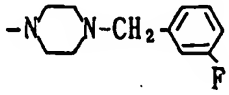
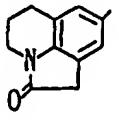
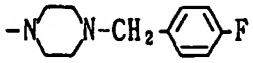
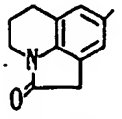
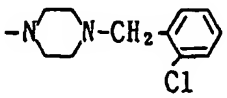
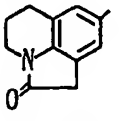
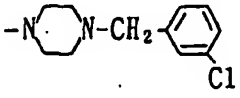
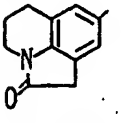
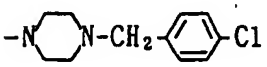
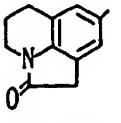
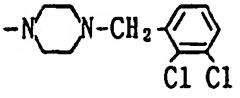
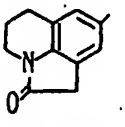
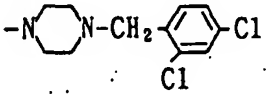
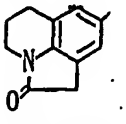
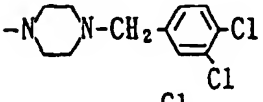
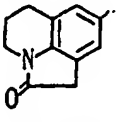
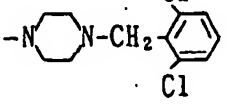
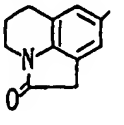
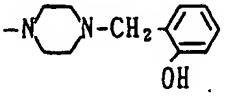
132		2	
133		2	
134		2	
135		2	
136		2	
137		2	
138		2	
139		2	
140		2	
141		2	
142		2	
143		2	

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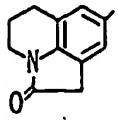
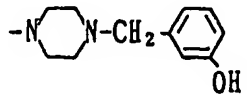
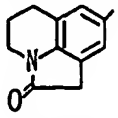
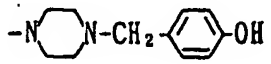
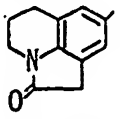
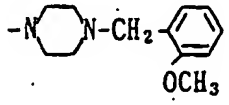
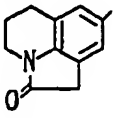
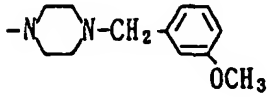
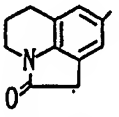
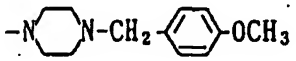
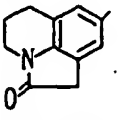
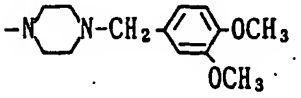
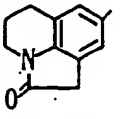
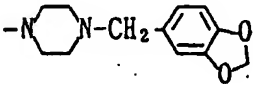
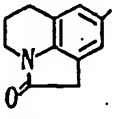
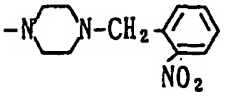
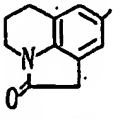
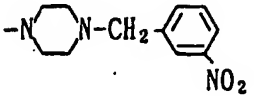
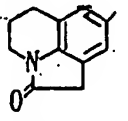
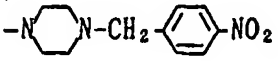
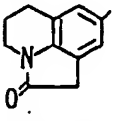
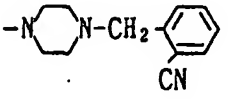
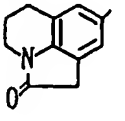
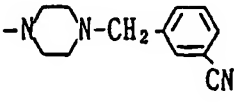
144		2	
145		2	
146		2	
147		2	
148		2	
149		2	
150		2	
151		2	
152		2	
153		2	
154		2	
155		2	

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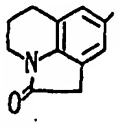
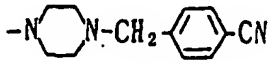
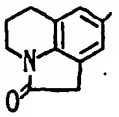
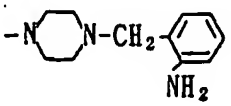
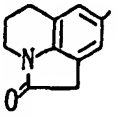
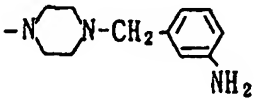
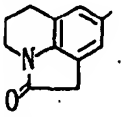
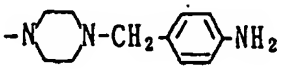
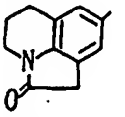
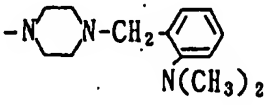
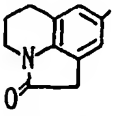
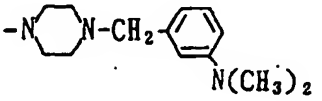
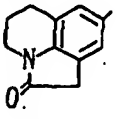
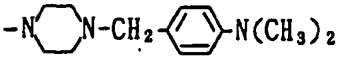
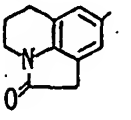
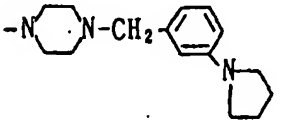
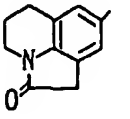
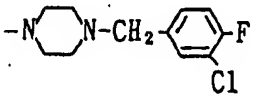
156		2	
157		2	
158		2	
159		2	
160		2	
161		2	
162		2	
163		2	
164		2	

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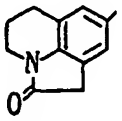
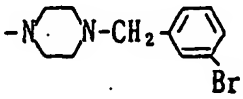
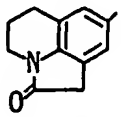
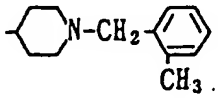
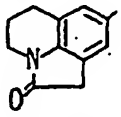
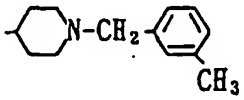
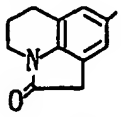
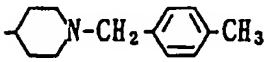
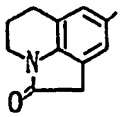
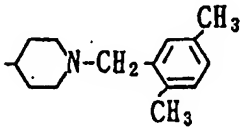
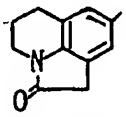
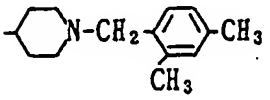
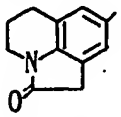
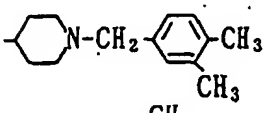
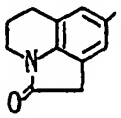
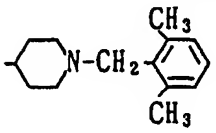
165		2	
166		2	
167		2	
168		2	
169		2	
170		2	
171		2	
172		2	

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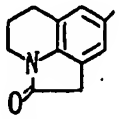
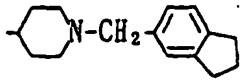
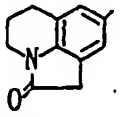
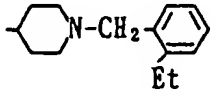
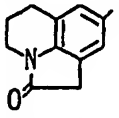
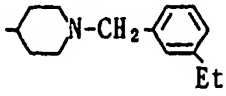
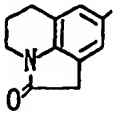
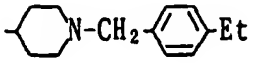
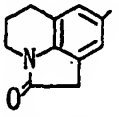
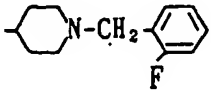
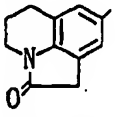
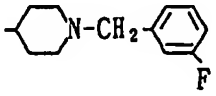
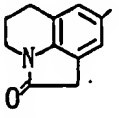
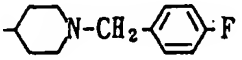
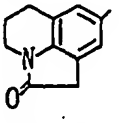
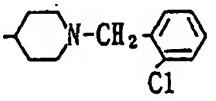
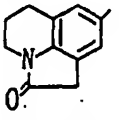
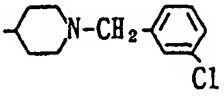
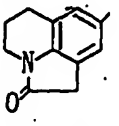
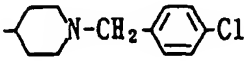
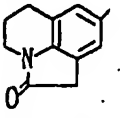
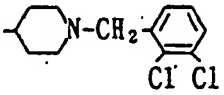
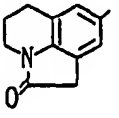
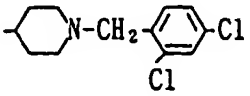
173		2	
174		2	
175		2	
176		2	
177		2	
178		2	
179		2	
180		2	
181		2	
182		2	
183		2	
184		2	

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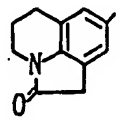
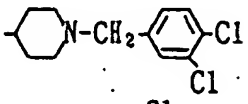
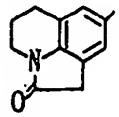
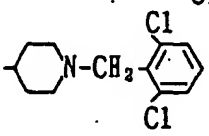
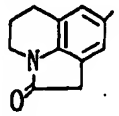
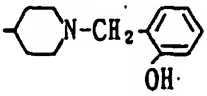
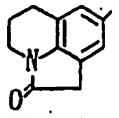
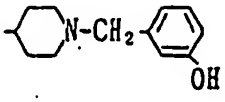
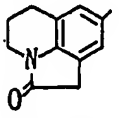
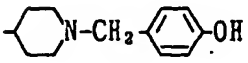
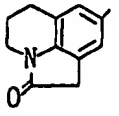
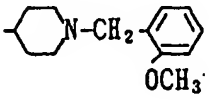
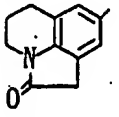
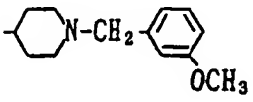
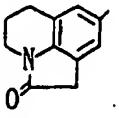
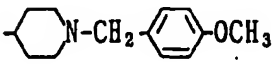
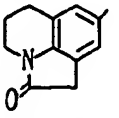
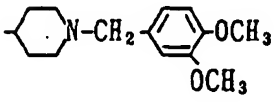
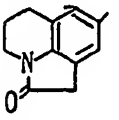
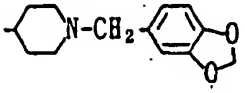
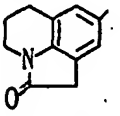
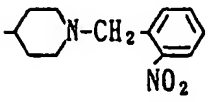
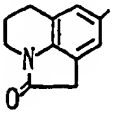
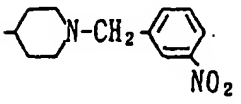
185		2	
186		2	
187		2	
188		2	
189		2	
190		2	
191		2	
192		2	
193		2	
194		2	
195		2	
196		2	

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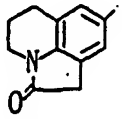
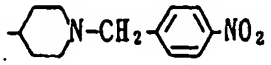
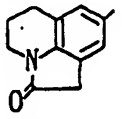
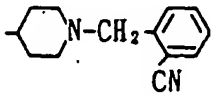
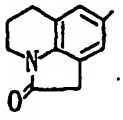
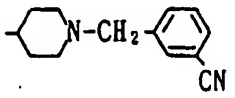
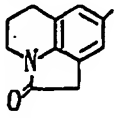
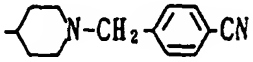
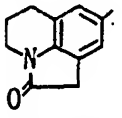
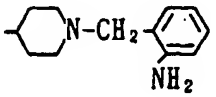
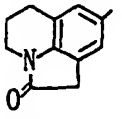
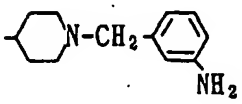
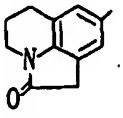
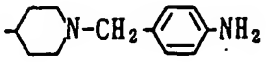
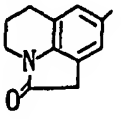
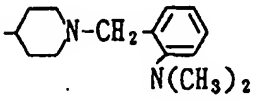
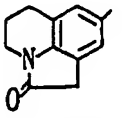
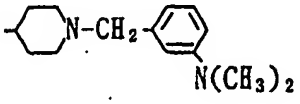
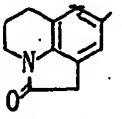
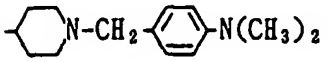
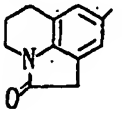
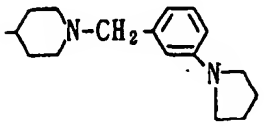
197		2	
198		2	
199		2	
200		2	
201		2	
202		2	
203		2	
204		2	
205		2	
206		2	
207		2	

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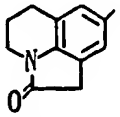
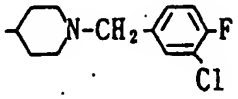
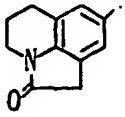
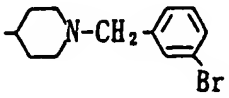
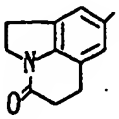
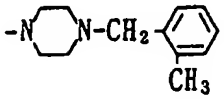
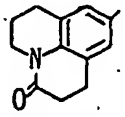
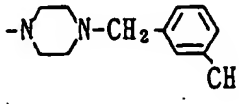
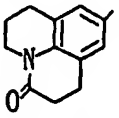
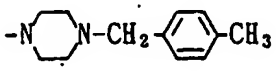
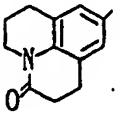
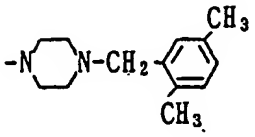
208		2	
209		2	
210		2	
211		2	
212		2	
213		2	

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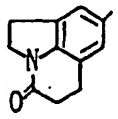
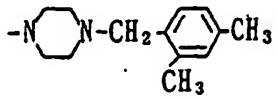
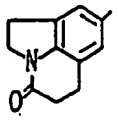
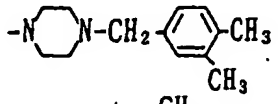
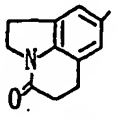
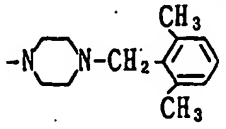
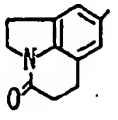
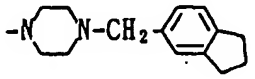
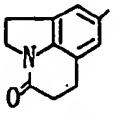
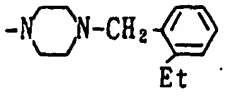
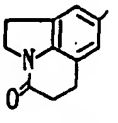
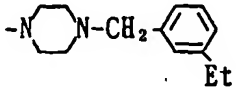
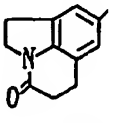
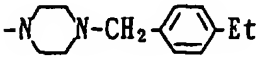
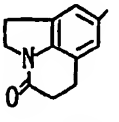
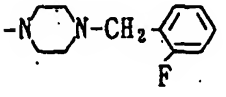
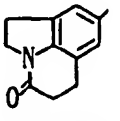
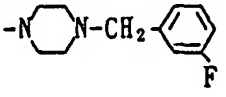
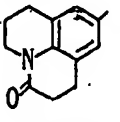
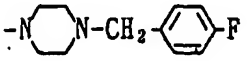
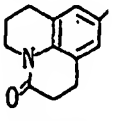
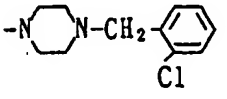
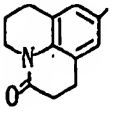
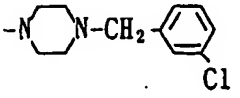
214		2	
215		2	
216		2	
217		2	
218		2	
219		2	
220		2	
221		2	
222		2	
223		2	
224		2	
225		2	

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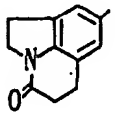
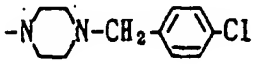
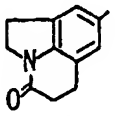
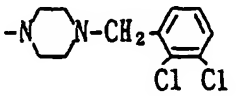
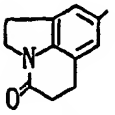
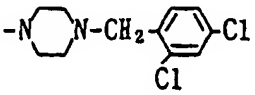
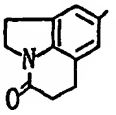
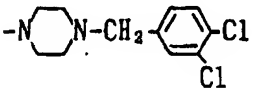
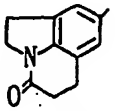
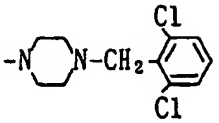
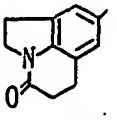
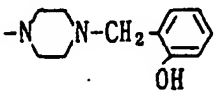
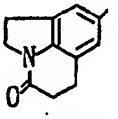
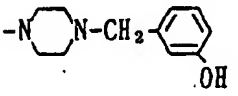
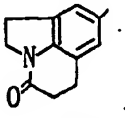
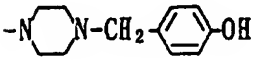
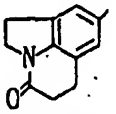
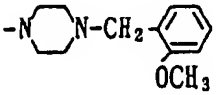
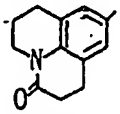
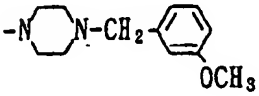
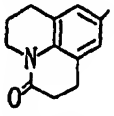
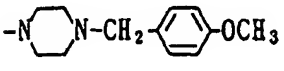
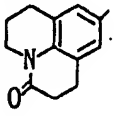
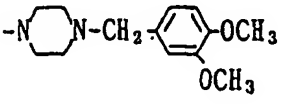
226		2	
227		2	
228		2	
229		2	
230		2	
231		2	
232		2	
233		2	
234		2	
235		2	
236		2	
237		2	

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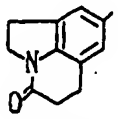
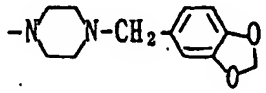
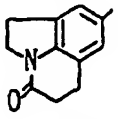
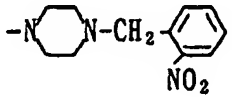
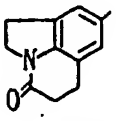
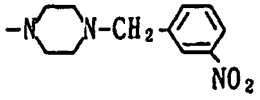
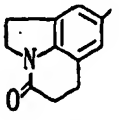
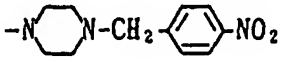
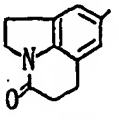
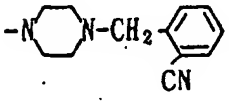
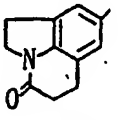
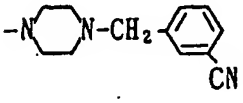
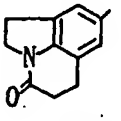
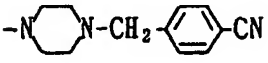
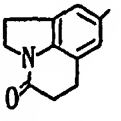
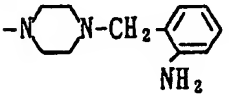
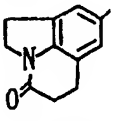
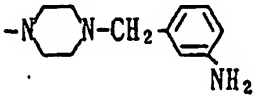
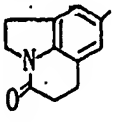
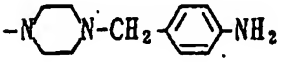
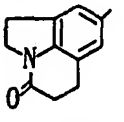
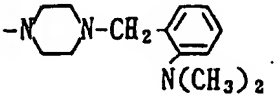
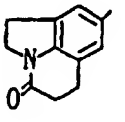
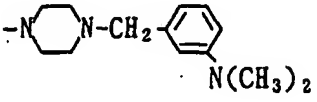
238		2	
239		2	
240		2	
241		2	
242		2	
243		2	
244		2	
245		2	
246		2	
247		2	
248		2	
249		2	

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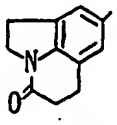
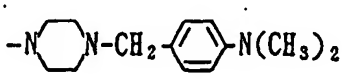
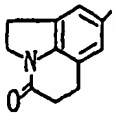
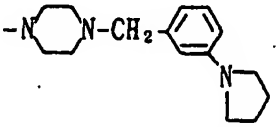
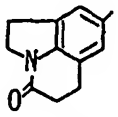
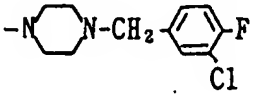
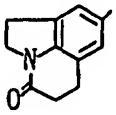
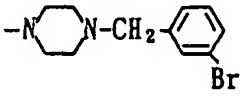
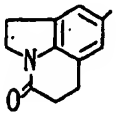
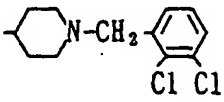
250		2	
251		2	
252		2	
253		2	
254		2	

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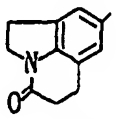
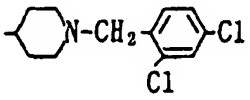
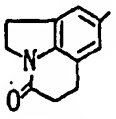
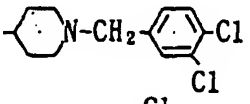
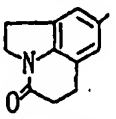
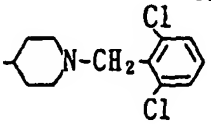
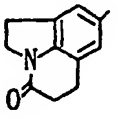
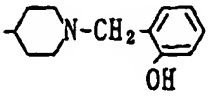
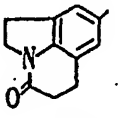
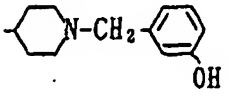
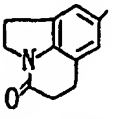
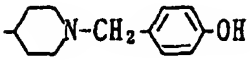
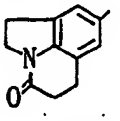
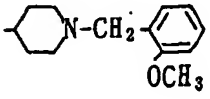
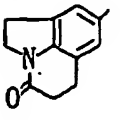
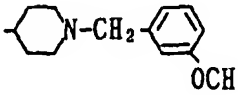
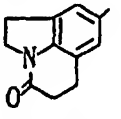
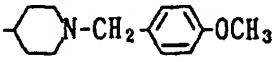
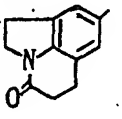
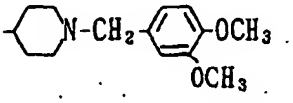
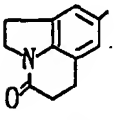
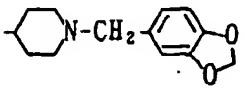
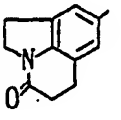
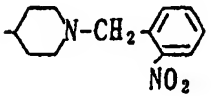
255		2	
256		2	
257		2	
258		2	
259		2	
260		2	
261		2	
262		2	
263		2	
264		2	
265		2	
266		2	

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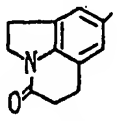
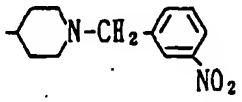
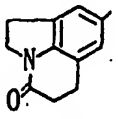
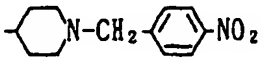
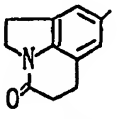
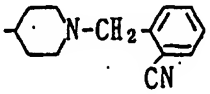
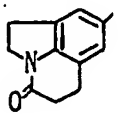
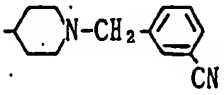
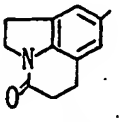
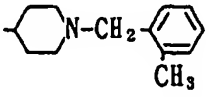
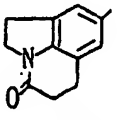
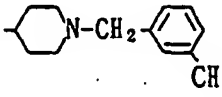
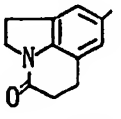
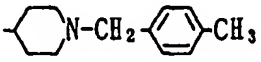
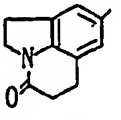
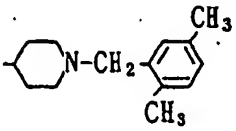
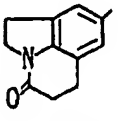
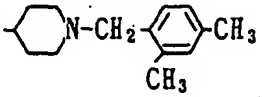
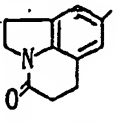
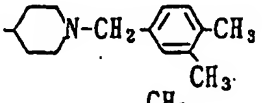
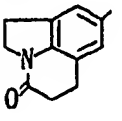
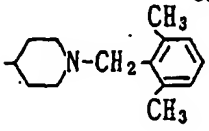
267		2	
268		2	
269		2	
270		2	
271		2	
272		2	
273		2	
274		2	
275		2	
276		2	
277		2	

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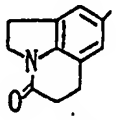
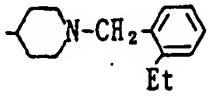
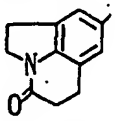
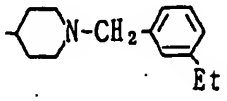
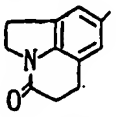
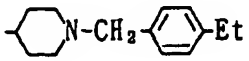
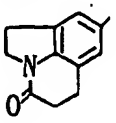
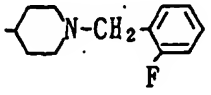
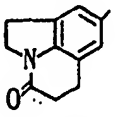
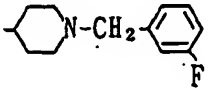
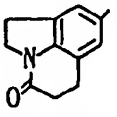
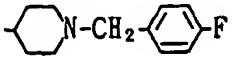
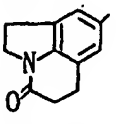
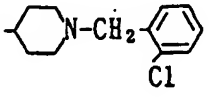
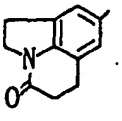
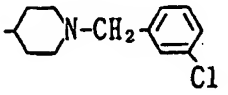
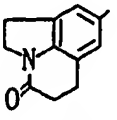
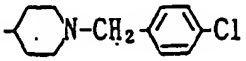
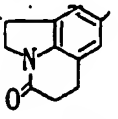
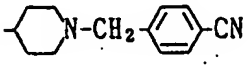
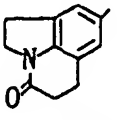
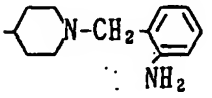
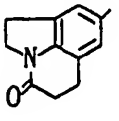
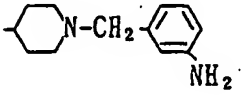
278		2	
279		2	
280		2	
281		2	
282		2	
283		2	
284		2	
285		2	
286		2	
287		2	
288		2	
289		2	

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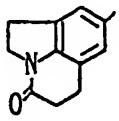
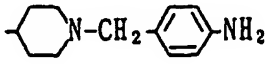
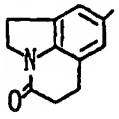
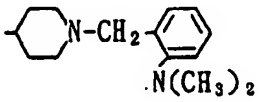
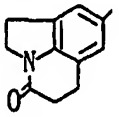
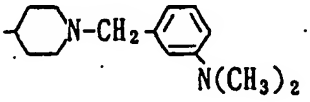
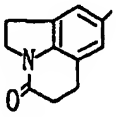
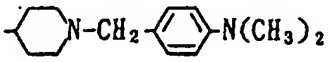
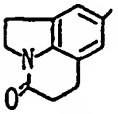
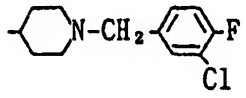
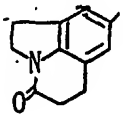
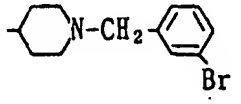
290		2	
291		2	
292		2	
293		2	
294		2	
295		2	

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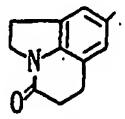
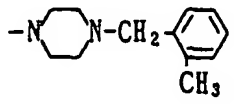
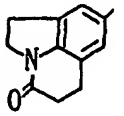
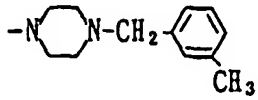
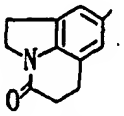
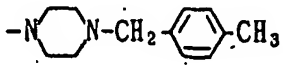
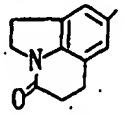
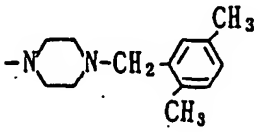
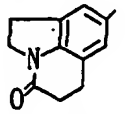
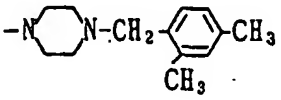
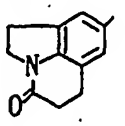
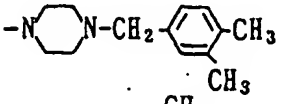
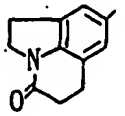
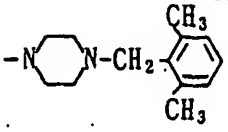
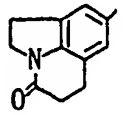
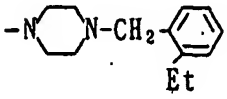
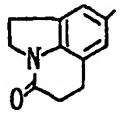
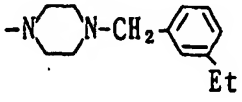
296		2	
297		2	
298		2	
299		2	
300		2	
301		2	
302		2	
303		2	
304		2	

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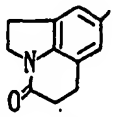
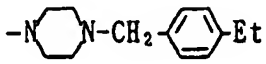
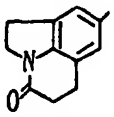
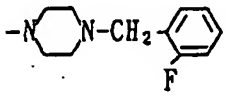
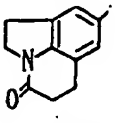
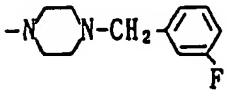
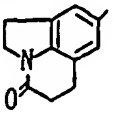
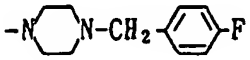
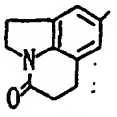
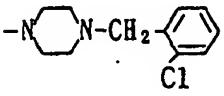
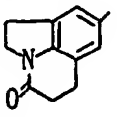
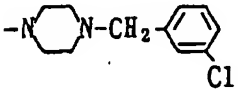
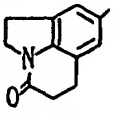
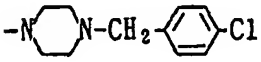
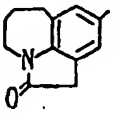
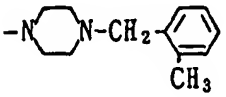
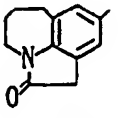
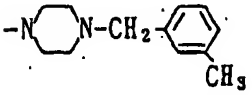
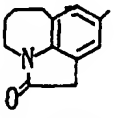
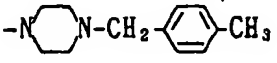
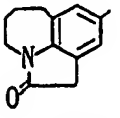
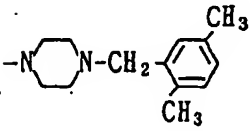
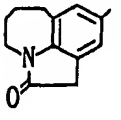
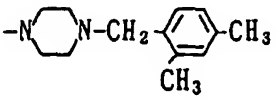
305		2	
306		2	
307		2	
308		2	
309		2	
310		2	
311		2	
312		2	
313		2	
314		2	
315		2	
316		2	

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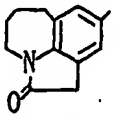
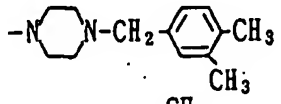
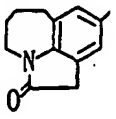
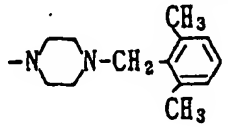
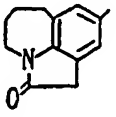
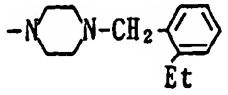
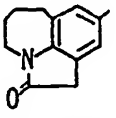
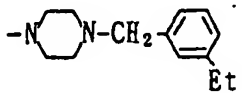
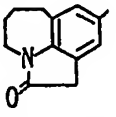
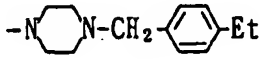
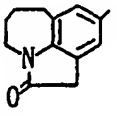
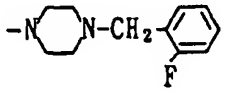
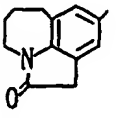
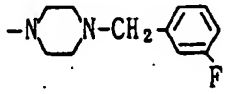
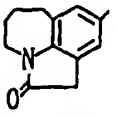
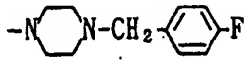
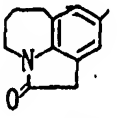
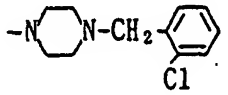
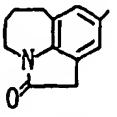
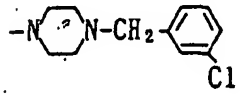
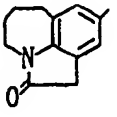
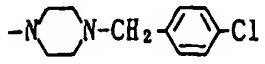
317		2	
318		2	
319		2	
320		2	
321		2	
322		2	
323		2	
324		2	
325		2	
326		2	
327		2	

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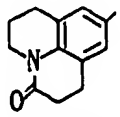
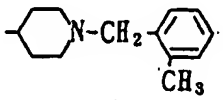
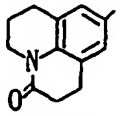
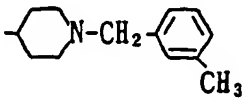
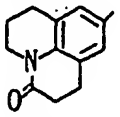
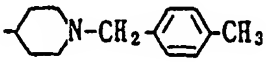
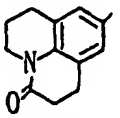
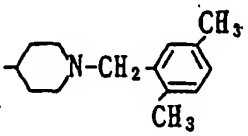
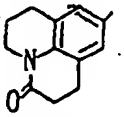
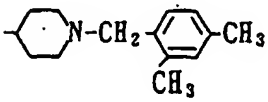
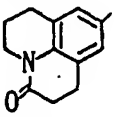
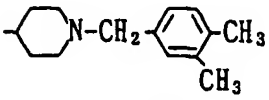
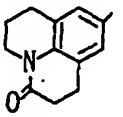
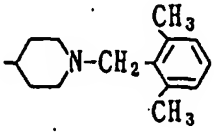
328		2	
329		2	
330		2	
331		2	
332		2	
333		2	
334		2	

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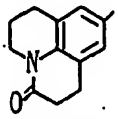
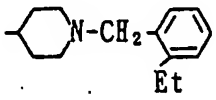
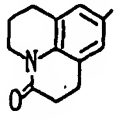
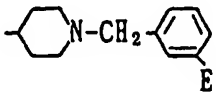
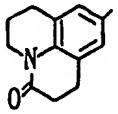
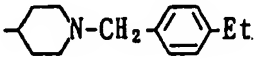
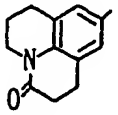
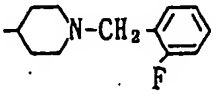
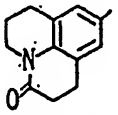
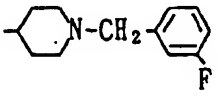
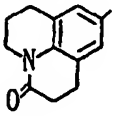
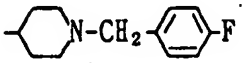
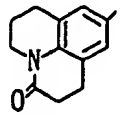
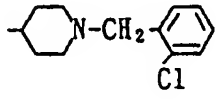
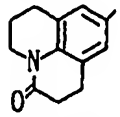
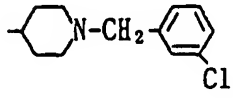
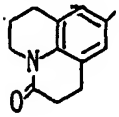
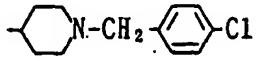
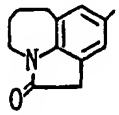
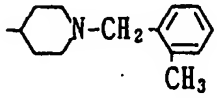
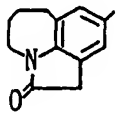
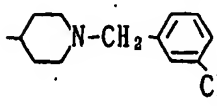
335		2	
336		2	
337		2	
338		2	
339		2	
340		2	
341		2	
342		2	
343		2	
344		2	
345		2	

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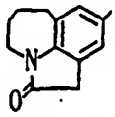
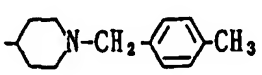
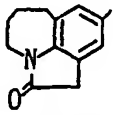
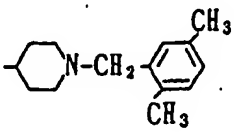
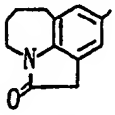
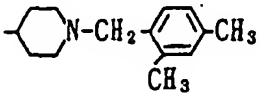
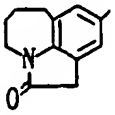
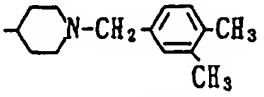
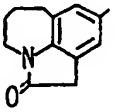
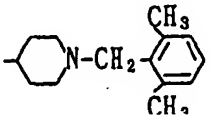
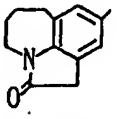
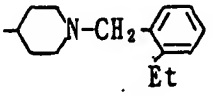
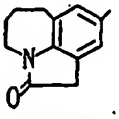
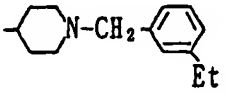
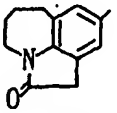
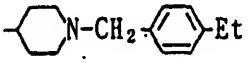
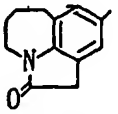
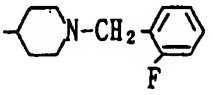
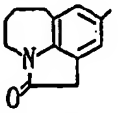
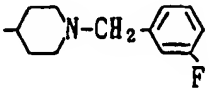
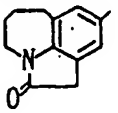
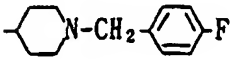
346		2	
347		2	
348		2	
349		2	
350		2	
351		2	
352		2	
353		2	
354		2	
355		2	
356		2	

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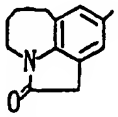
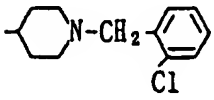
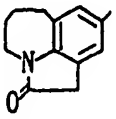
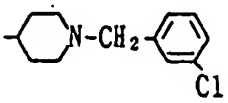
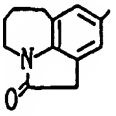
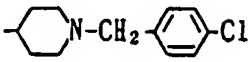
357		2	
358		2	
359		2	

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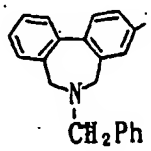
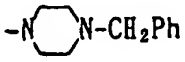
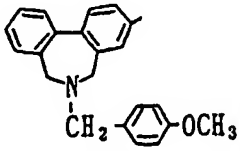
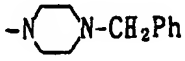
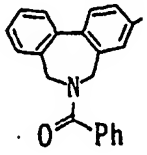
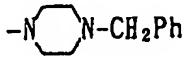
360		2	
361		2	
362		2	

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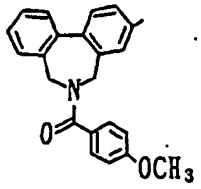
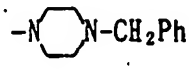
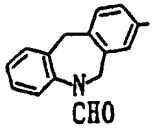
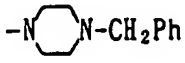
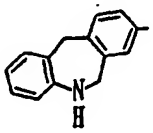
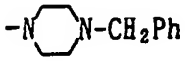
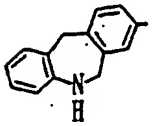
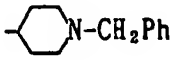
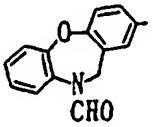
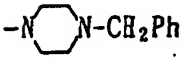
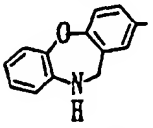
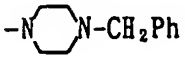
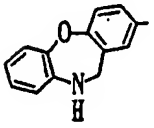
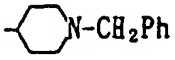
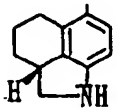
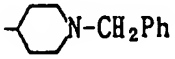
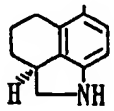
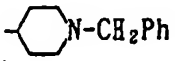
362		2	
363		2	
364		2	
364		2	
365		2	
366		2	
367		2	
368		2	
369		2	

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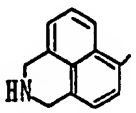
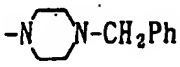
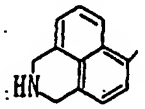
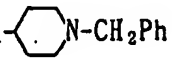
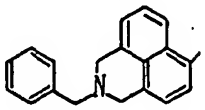
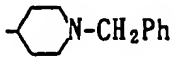
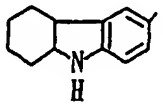
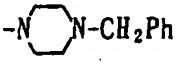
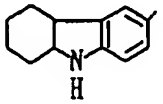
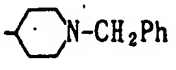
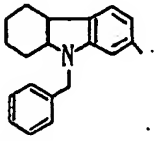
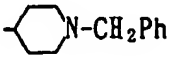
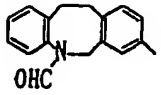
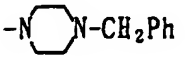
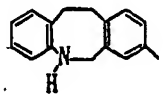
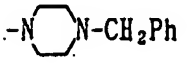
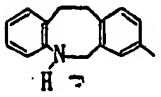
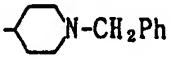
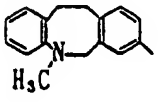
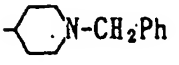
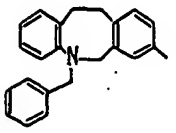
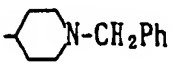
370		2	
371		2	
372		2	
373		2	
374		2	
375		2	
376		2	
377		2	
378		2	
379		2	
380		2	

[0034] In the above tables, Ac represents an acetyl group; Et represents an ethyl group; Ph represents a phenyl group.

[0035] It is preferable that salts of the compound (I) be physiologically acceptable acid adduct salts. Such salts include salts with inorganic acids (e.g., hydrochloric acid, phosphoric acid, hydrobromic acid, sulfuric acid) and salts with organic acids (e.g., acetic acid, formic acid, propionic acid, fumaric acid, maleic acid, succinic acid, tartaric acid, citric acid, malic acid, oxalic acid, benzoic acid, methanesulfonic acid, benzenesulfonic acid).

[0036] A method of producing the compound (I) or a salt thereof is hereinafter described in detail.

[0037] Although the following description of the production process is applicable not only to the compound (I) itself but also to the above-described salt thereof, the salt is also referred to as the compound (I) in the description below.

[0038] The compound (I) can be produced by reacting a compound represented by the formula:

$$Ar\text{-}H \qquad (II)$$

wherein the symbols have the same definitions as above or a salt thereof, and a compound (or salt thereof) represented by the formula:

$$Z^1\text{—}\overset{\overset{O}{\|}}{C}\text{—}(CH_2)_n\text{—}Y \qquad (III)$$

wherein Z^1 represents a leaving group; the other symbols have the same definitions as above or a salt thereof.

[0039] The leaving group for Z^1 is exemplified by halogen atoms (e.g., chlorine, bromine and iodine), $C_{1\text{-}6}$ alkylsulfonyloxy groups (e.g., methanesulfonyloxy, ethanesulfonyloxy) and $C_{6\text{-}10}$ arylsulfonyloxy groups (e.g., benzenesulfonyloxy, p-toluenesulfonyloxy), with preference given to halogen atoms (e.g., chlorine) and others.

[0040] The compound (II) or a salt thereof can be produced by known methods or modifications thereof such as the methods described in the Journal of Chemical Society, 1381 (1949), the Canadian Journal of Chemistry, 42, 2904 (1964), the Journal of Organic Chemistry, 28, 3058 (1963), the Journal of American Chemical Society, 76, 3194 (1954), 87, 1397 (1965), 88, 4061 (1966) and Japanese Patent Unexamined Publication No. 41539/1974.

[0041] The compound (III) or a salt thereof can be produced by known methods or modifications thereof such as the methods described in the Chemical Pharmaceutical Bulletin, 34, 3747-3761 (1986) and EP-A-0,378,207.

[0042] Salts of the compounds (II) and (III) include salts with inorganic acids (e.g., hydrochloric acid, phosphoric acid, hydrobromic acid, sulfuric acid) and salts with organic acids (e.g., acetic acid, formic acid, propionic acid, fumaric acid, maleic acid, succinic acid, tartaric acid, citric acid, malic acid, oxalic acid, benzoic acid, methanesulfonic acid, benzenesulfonic acid).

[0043] The reaction between the compound (III) or a salt thereof and the compound (II) or a salt thereof can be carried out by, for example, reacting them in the absence of a solvent or in a solvent as necessary. Any solvent for ordinary chemical represents can be used for this reaction, as long as the reaction is not interfered with. Such solvents include organic solvents such as hydrocarbon solvents (e.g., pentane, hexane, benzene, toluene, nitrobenzene), halogenated hydrocarbon solvents (e.g., dichloromethane, chloroform, 1,2-dichloroethane, carbon tetrachloride), ether solvents (e.g., ethyl ether, tetrahydrofuran, dioxane, dimethoxyethane), nitroalkanes (e.g., nitromethane, propionitrile), and carbon disulfide, with preference given to dichloromethane, 1,2-dichloroethane, nitrobenzene, carbon disulfide and others. The amount of solvent used is normally 0.5 to 100 ml, preferably 5 to 20 ml per mmol of the compound (III) or a salt thereof. Reaction temperature is normally -30 to 150°C, preferably 20 to 100°C. Reaction time is normally 0.5 to 72 hours, preferably 1 to 16 hours.

[0044] Lewis acids for this reaction include aluminum chloride, aluminum bromide, zinc chloride, titanium chloride, tin (IV) chloride, boron trifluoride, iron (II) chloride, iron (III) chloride, antimony (V) pentachloride, bismuth (III) chloride, mercury (II) chloride, hydrogen fluoride, sulfuric acid and polyphosphoric acid, with preference given to aluminum chloride and others. The amount of Lewis acid used is normally 1 to 10 mol, preferably 2 to 10 mol per mol of the compound (III) or a salt thereof. The amount of the compound (II) or a salt thereof used is normally 1 to 20 mol, preferably 1 to 5 mol per mol of the compound (III) or a salt thereof.

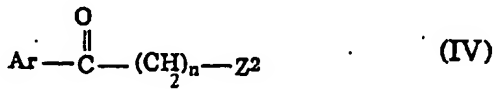
[0045] In the above reaction, the position at which the following group:

$$-\overset{\overset{O}{\|}}{C}\text{—}(CH_2)_n\text{—}Y$$

in the compound (III) or a salt thereof is introduced to the compound (II) or a salt thereof may be any one of the possible

positions of substitution in ring A. However, when the compound (II) or a salt thereof has a 1,2,2a,3,4,5-hexahydrobenz [cd]indole skeleton (provided that ring A has no substituent), it is introduced mainly at the 6-position. However, compounds having an introduction at other positions (7- and 8-positions) may be produced and separated.

[0046] Also, by reacting a compound represented by the formula:

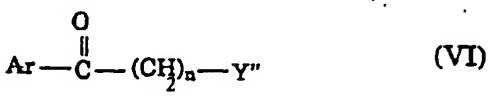


(IV)

wherein the symbols have the same definitions as above or a salt thereof, and a compound represented by the formula:

$$Z^3\text{-}Y'' \qquad (V)$$

wherein the symbols have the same definitions as above or a salt thereof, a compound represented by the formula:



(VI)

wherein the symbols have the same definitions as above or a salt thereof, can be produced.

[0047] Z^2 and Z^3 independently represent a group capable of splitting off upon reaction therebetween.

[0048] The leaving group for Z^2 is exemplified by halogen atoms (e.g., chlorine, bromine and iodine), $C_{1\text{-}6}$ alkylsulfonyloxy groups (e.g., methanesulfonyloxy, ethanesulfonyloxy) and $C_{6\text{-}10}$ arylsulfonyloxy groups (e.g., benzenesulfonyloxy, p-toluenesulfonyloxy), with preference given to halogen atoms. More specifically, Z^2 is preferably a halogen atom such as an atom of chlorine or bromine.

[0049] The leaving group for Z^3 is exemplified by hydrogen atom, trialkylsilyl groups (e.g., trimethylsilyl, triethylsilyl, t-butyldimethylsilyl) and metal atoms (e.g., atoms of sodium, potassium and lithium). A hydrogen atom, in particular, is often used.

[0050] Salts of the compound (VI) are exemplified by the same salts as specified for the compound (I).

[0051] Salts of the compounds (IV) and (V) include salts with inorganic acids (e.g., hydrochloric acid, phosphoric acid, hydrobromic acid, sulfuric acid) and salts with organic acids (e.g., acetic acid, formic acid, propionic acid, fumaric acid, maleic acid, succinic acid, tartaric acid, citric acid, malic acid, oxalic acid, benzoic acid, methanesulfonic acid, benzenesulfonic acid).

[0052] The amount of the compound (V) or a salt thereof used for this reaction is normally 1.0 to 50.0 mol, preferably 1.0 to 10.0 mol per mol of the compound (IV) or a salt thereof. This reaction can be carried out under cooling or heating conditions (0 to 120°C). Reaction time is normally 10 minutes to 48 hours, preferably 2 to 16 hours.

[0053] Although this reaction can be carried out in the absence of a solvent, it may be carried out in a solvent as necessary. Any solvent can be used for this reaction, as long as the reaction is not interfered with. Such solvents include lower alcohols such as methanol, ethanol, propanol, isopropanol, n-butanol and t-butanol, ethers such as dioxane, ether and tetrahydrofuran, aromatic hydrocarbons such as toluene, benzene and xylene, halogenated hydrocarbons such as dichloromethane, 1,2-dichloroethane, amides such as dimethylformamide, dimethylacetamide and hexamethylphosphonotriamide, and esters such as ethyl acetate and butyl acetate. The amount of solvent used is normally 0.5 to 100 ml, preferably 5 to 20 ml per mmol of the compound (IV-a) or a salt thereof.

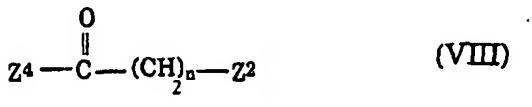
[0054] This reaction can be carried out in the presence of a base as necessary. Bases for this purpose include inorganic bases such as sodium carbonate, potassium carbonate, lithium carbonate, sodium hydroxide, potassium hydroxide, sodium methoxide, sodium ethoxide and sodium hydride, and organic bases such as pyridine, 4-dimethylaminopyridine and triethylamine. The amount of base used is normally 1 mol or more, preferably 1.0 to 5.0 mol per mol of the compound (V) or a salt thereof.

[0055] Also, this reaction may be accelerated as appropriate in the presence of an iodide (e.g., sodium iodide, potassium iodide, lithium iodide). In this case, the amount of iodide used is normally 1 to 5 mol, preferably 1.0 to 1.5 mol per mol of the compound (IV) or a salt thereof.

[0056] The starting material compound (IV) or a salt thereof can be produced by, for example, reacting a compound represented by the formula:

Ar-H (II)

wherein the symbols have the same definitions as above or a salt thereof, and a compound represented by the formula:



(VIII)

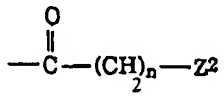
wherein Z^4 represents a leaving group; the other symbols have the same definitions as above or a salt thereof.

[0057] The leaving group for Z^4 is exemplified by halogen atoms (e.g., atoms of chlorine, bromine and iodine), C_{1-6} alkylsulfonyloxy groups (e.g., methanesulfonyloxy, ethanesulfonyloxy) and C_{6-10} arylsulfonyloxy groups (e.g., benzenesulfonyloxy, p-toluenesulfonyloxy), with preference given to halogen atoms (e.g., chlorine atom) etc.

[0058] The compound (VIII) can be produced by known methods or modifications thereof.

[0059] . The reaction between the compound (II) or a salt thereof and the compound (VIII) or a salt thereof can be carried out under, for example, the same conditions as for the reaction between the compound (II) or a salt thereof and the compound (III) or a salt thereof.

[0060] In the above reaction, the position at which the following group:



in the compound (VIII) is introduced to the compound (II) or a salt thereof may be any one of the possible positions of substitution in ring A. However, when the compound (II) or a salt thereof has a 1,2,2a,3,4,5-hexahydrobenz[cd]indole skeleton (provided that ring A has no substituent), it is introduced mainly at the 6-position. However, compounds having an introduction at other positions (7- and 8-positions) may be produced and separated.

[0061] The compound (IV) or a salt thereof thus obtained may be isolated and purified by known means such as concentration, liquid property conversion, redissolution, solvent extraction, fractional distillation, distillation, crystallization, recrystallization and chromatography, or may be used in the form of a reaction mixture as such, without isolation, as a starting material for the next process.

[0062] The starting material compound (V) or a salt thereof can be produced by known methods or modifications thereof.

[0063] With respect to the above reactions, provided that the starting material compound has an amino group, a hydroxyl group or another group as a substituent therefor, such substituent may have a protecting group in common use in peptide chemistry etc. as introduced therein. The desired compound can be obtained by removing the protecting group as necessary upon completion of the reaction.

[0064] Protecting groups for the amino group include C_{1-6} alkyl-carbonyl groups which may have a substituent (e.g., formyl, acetyl, ethylcarbonyl), benzoyl, C_{1-6} alkyl-oxycarbonyl groups (e.g., methoxycarbonyl, ethoxycarbonyl), phenyloxycarbonyl groups (e.g., phenoxycarbonyl), C_{7-15} aralkyloxy-carbonyl groups (e.g., benzyloxycarbonyl, fluorenyloxycarbonyl), trityl and phthaloyl. Substituents for these protecting groups include halogen atoms (e.g., fluorine, chlorine, bromine and iodine), C_{1-6} alkylcarbonyl groups (e.g., methylcarbonyl, ethylcarbonyl, butylcarbonyl) and nitro group, the number of substituents being 1 to 3.

[0065] Protecting groups for the hydroxyl group include C_{1-6} alkyl groups which may have a substituent (e.g., methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl), phenyl, C_{7-10} aralkyl groups (e.g., benzyl), C_{1-6} alkylcarbonyl groups (e.g., formyl, acetyl, ethylcarbonyl), phenyloxycarbonyl groups (e.g., phenoxycarbonyl), C_{7-10} aralkyl-carbonyl groups (e.g., benzyloxycarbonyl), pyranyl, furanyl and silyl. Substituents for these protecting groups include halogen atoms (e.g., fluorine, chlorine, bromine and iodine), C_{1-6} alkyl groups, phenyl, C_{7-10} aralkyl groups and nitro group, the number of substituents being 1 to 4.

[0066] These protecting groups can be removed by known methods or modifications thereof, including treatments with acid, base, reducing agents, ultraviolet rays, hydrazine, phenylhydrazine, sodium N-methyldithiocarbamate, tetrabutylammonium fluoride and palladium acetate.

[0067] When the compound (I), or (VI) or a salt thereof thus obtained has an acylamino group which may have a substituent, it can be converted to a compound or a salt thereof having a primary or secondary amino group by dea-

cylation. The starting material compound (I), or (VI) or a salt thereof having an acylamino group which may have a substituent may be as isolated and purified by known means such as concentration, liquid property conversion, redissolution, solvent extraction, fractional distillation, distillation, crystallization, recrystallization and chromatography, or may be used in the form of a reaction mixture as such, without isolation, as a starting material. Accordingly, the compound (I) or (VI) or a salt thereof having an acylamino group which may have a substituent is kept at a temperature of normally 10 to 150°C, preferably 50 to 100°C, in an aqueous solution of an acid such as a mineral acid (e.g., nitric acid, hydrochloric acid, hydrobromic acid, iodic acid, sulfuric acid) or a base such as an alkali metal hydroxide (e.g., sodium hydroxide, potassium hydroxide, barium hydroxide, lithium hydroxide). The amount of such acid or base used is normally 1 to 100 mol, preferably 1 to 40 mol per mol of the compound (XII) or a salt thereof. The strength of acid or base is normally about 0.1 to 10 N, preferably 2 to 10 N. Although varying depending on reaction temperature, reaction time is normally 1 to 24 hours, preferably 2 to 10 hours.

[0068] Thus-obtained compound (I) or (VI) or a salt thereof having a primary or secondary amino group which may have a substituent may have a hydrocarbon group which may have a substituent introduced to the primary or secondary amino group thereof, to yield the compound (I) or (VI) or a salt thereof having an amino group substituted for by a hydrocarbon group which may have a substituent. The starting material compound (I) or (VI) or or a salt thereof having an primary or secondary amino group may be used after isolation and purification by known means such as concentration, liquid property conversion, redissolution, solvent extraction, fractional distillation, distillation, crystallization, recrystallization and chromatography, or may be used in the form of a reaction mixture as such, without isolation, as a starting material. Accordingly, the compound (I), or (VI) or a salt thereof having an amino group substituted by a $C_{1\text{-}6}$ alkyl group can also be produced by reaction between the compound (I), or (VI) or a salt thereof having a primary or secondary amino group and a compound represented by the formula:

$$R^7\text{-}Z^3 \qquad \text{(XIII)}$$

wherein R^7 represents a $C_{1\text{-}6}$ alkyl group; Z^3 represents a leaving group.

[0069] The $C_{1\text{-}6}$ alkyl group for R^7 is exemplified by the same alkyl groups as specified for R^2, R^3 or R^6 above.

[0070] The leaving group for Z^3 is exemplified by halogen atoms (e.g., chlorine, bromine and iodine), $C_{1\text{-}6}$ alkylsulfonyloxy groups (e.g., methanesulfonyloxy, ethanesulfonyloxy) and $C_{6\text{-}10}$ arylsulfonyloxy groups (e.g., benzenesulfonyloxy and p-toluenesulfonyloxy), with preference given to halogen atoms (e.g., chlorine).

[0071] This reaction can be carried out in the presence or absence of a solvent, with a base added as necessary. Bases for this purpose include inorganic bases such as sodium carbonate, potassium carbonate, lithium carbonate, sodium hydroxide, potassium hydroxide, sodium methoxide, sodium ethoxide and sodium hydride, and organic bases such as pyridine, 4-dimethylaminopyridine and triethylamine. Any solvent can be used, as long as it does not interfere with the reaction, such solvents include lower alcohols such as methanol, ethanol, propanol, isopropanol, n-butanol and t-butanol, ethers such as dioxane, ether and tetrahydrofuran, aromatic hydrocarbons such as toluene, benzene and xylene, halogenated hydrocarbons such dichloromethane, 1,2-dichloroethane, amides such as dimethylformamide, dimethylacetamide and hexamethylphosphonotriamide, and esters such as ethyl acetate and butyl acetate. This reaction can be carried out under cooling conditions (0 to 10°C), at room temperature (10 to 40°C) or under heating conditions (40 to 120°C). Reaction time is normally 10 minutes to 48 hours, preferably 2 to 16 hours. The amount of compound (XIII) used is preferably 0.3 to 5.0 mol per mol of the compound (I'), (VI) or (IX) or a salt thereof having a primary or secondary amino group. The amount of base used is normally 1 or more mol, preferably 1.1 to 5 mol per mol of the compound (I) or (VI) or a salt thereof having a primary or secondary amino group.

[0072] Also, this reaction may be accelerated as appropriate in the presence of an iodide such as sodium iodide, potassium iodide or lithium iodide. In this case, the amount of iodide used is normally 1 to 5 mol, preferably 1.1 to 1.5 mol per mol of the compound (XI).

[0073] The compound (XIII) can be produced by known method or modifications thereof.

[0074] The compound (I) can be converted to a salt by a conventional method when it is in a free form, and can be converted to a free form or another salt by a conventional method when it is in a salt form. The compound (I) or a salt thereof can be isolated and purified by known methods as described above. Also, the compound (I) or a salt thereof involves steric isomers based on the presence of asymmetric carbon atoms. These isomers can also be isolated and purified by known methods as described above or other methods such as fractional recrystallization, and chromatography using optically active columns.

[0075] The compound (I) or a salt thereof acts on the central nervous system of mammals, potently inhibits cholinesterase and exhibit excellent antiamnestic effects on various amnesia inducing actions in humans or animals (e.g., mice). Further, the compound (I) or salts thereof has monoamine (e.g. norepinephirine, serotonin, etc.) reuptake inhibitory activity, and exhibit excellent antidepressant activity, etc. in humans or animals (e.g. mice).

[0076] The compound (I) or a salt thereof is remarkably excellent in separation of effects on central nervous system from those on peripheral nervous system, as compared with physostigmine and, at the anti-amnestic and antidepressant dose level, do not cause peripheral nervous system effects such as spasm, salivation, diarrhea, etc., with prolonged duration of action and with low toxicity, and they exhibit marked effect in oral administration. The acute toxicity (LD_{50}) of the compound (I) or a salt thereof exceeds 100 mg/kg.

[0077] For these reasons, the compound of the present invention serves well as a safe brain function improving drug in mammals, including humans.

[0078] Diseases against which the compound of the present invention is effective include senile dementia, Alzheimer's disease, Huntington's chorea, hyperkinesis and mania. The inventive compound can be used to prevent or treat these diseases.

[0079] The compound of the present invention can be orally or non-orally administered to mammals, including humans, normally in the form of a pharmaceutical preparation with a pharmaceutically acceptable carrier or excipient.

[0080] Acceptable dosage forms are oral preparations (e.g., powders, tablets, granules, capsules) and non-oral preparations (e.g., suppositories, injectable preparations). These preparations can be prepared by known methods. Although varying depending on type of disease, symptoms and other factors, ordinary daily dose for oral administration is 0.01 mg to 50 mg, preferably 0.1 to 30 mg, more preferably 0.5 to 10 mg for an adult weighing 70 kg.

[0081] The present invention is hereinafter described in more detail by means of the following working examples, reference examples, formulation examples and an experimental example.

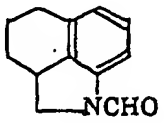
[0082] Elution in column chromatography in the experimental and reference examples was conducted with observation by TLC (thin layer chromatography), unless otherwise stated. In the TLC observations, TLC was conducted on a TLC plate of Merck $60F_{254}$, in which the developing solvent was the same as the column chromatography eluent and the detector was a UV detector. Also, 48% HBr was sprayed over the spot on the TLC plate, followed by thermal hydrolysis, after which the ninhydrin reagent was sprayed, followed by heating. When the response is positive, a red to red-purple color should develop. Using this phenomenon in combination with UV detection, the eluted fraction containing the desired product was confirmed and collected. The column packing silica gel was Merck Kiesel Gel 60 (70-230 mesh), unless otherwise stated.

[0083] "Normal temperature" or "room temperature" is generally defined to be between 5°C and 40°C, "normal pressure" meaning a pressure of about 1 atm. Also, % is percent by weight unless otherwise stated, and $C_4H_4O_4$ indicates fumaric acid.

Reference Example 1

1-Formyl-1,2,2a,3,4,5-hexahydrobenz[cd]indole

[0084]



(1) A mixture of 5.0 g of 1-benzoyl-1,2,2a,3,4,5-hexahydrobenz[cd]indol-5-one, 2.7 g of potasslum hydroxide, 2 ml of hydrazine hydrate and 20 ml of ethylene glycol was heated at 120°C for 2 hours and then at 190°C for 3 hours. After mixture cooling, water was added, and the reaction product was extracted with dichloromethane. After the extract was dried over magnesium sulfate, the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (developing solvent: dichloromethane-ethyl acetate = 10:1 (v/v)) to yield 1.9 g of 1,2,2a,3,4,5-hexahydrobenz[cd]indole as a colorless crystal having a melting point of 58 to 59°C.

Elemental analysis (for $C_{11}H_{13}N$):			
Calculated	C, 82.97;	H, 8.23;	N, 8.80
Found	C, 83.02;	H, 8.18;	N, 8.80

(2) To 18 ml of formic acid, 6 ml of acetic anhydride was added dropwise, followed by stirring at room temperature for 20 minutes. After a solution of 1.6 g of 1,2,2a,3,4,5-hexahydrobenz[cd]indole as obtained in (1) above in 2 ml of dichloromethane was added, the mixture was stirred at room temperature for 30 minutes. After water was added

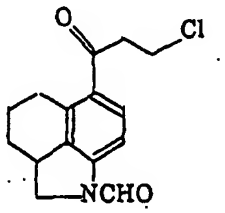
to the reaction mixture, the reaction product was extracted with dichloromethane. The extract was washed by sequential additions of a 5% aqueous sodium hydroxide solution and water, after which the solvent was distilled off under reduced pressure. The resulting crystal was recrystallized from dichloromethane-ether to yield the title compound as a colorless crystal having a melting point of 93 to 94°C.

Elemental analysis (for $C_{12}H_{13}NO$):			
Calculated	C, 76.98;	H, 7.00;	N, 7.48
Found	C, 76.94;	H, 7.01;	N, 7.52

Reference Example 2

3-Chloro-(1-formyl-1,2,2a,3,4,5-hexahydrobenz[cd]indol-6-yl)-1-propanone

[0085]



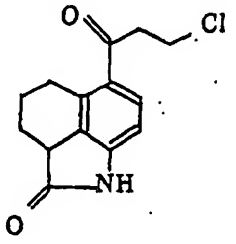
[0086] To a 10 ml solution of 0.8 g of 1-formyl-1,2,2a,3,4,5-hexahydrobenz[cd]indole as obtained in Reference Example 1 and 0.55 g of 3-chloropropionyl chloride in 10 ml of 1,2-dichloroethane, 1.4 g of aluminum chloride was added portionwise, followed by stirring at room temperature for 4 hours. The reaction mixture was poured over ice water, and the reaction product was extracted with dichloromethane. After the extract was dried over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (developing solvent: hexane-ethyl acetate-dichloromethane = 10:3:1 (v/v)) to yield 0.7 g of the title compound as a colorless crystal having a melting point of 82 to 85°C.

Elemental analysis (for $C_{15}H_{16}ClNO_2$):			
Calculated	C, 64.87;	H, 5.81;	N, 5.04
Found	C, 64.98;	H, 5.84;	N, 4.99

Reference Example 3

3-Chloro-1-(2-oxo-1,2,2a,3,4,5-hexahydrobenz[cd]indol-6-yl)-1-propanone

[0087]



[0088] Using 2a,3,4,5-tetrahydrobenz[cd]indol-2(1H)-one and 3-chloropropionyl chloride, the same procedure as in

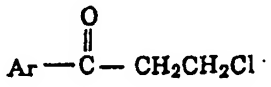
Reference Example 2 was followed, to yield the title compound as a colorless needle crystal having a melting point of 175 to 178°C.

Elemental analysis (for $C_{14}H_{14}ClNO_2$):			
Calculated	C, 63.76;	H, 5.35;	N, 5.31
Found	: C, 63.58;	H, 5.29;	N, 5.33

Reference Example 4

[0089] Using known tricyclic condensed heterocyclic rings and 3-chloropropionyl chloride, the same procedure as in Reference Example 2 was followed, to yield the compounds listed in Table 52.

Table 52.



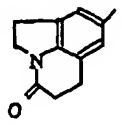
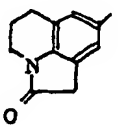
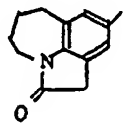
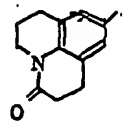
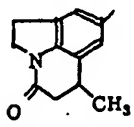
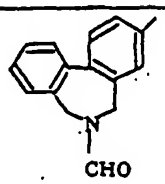
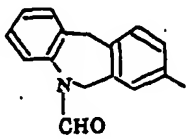
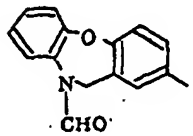
Comp. No.	Ar	Melting Point (°C)	Molecular Formula	Elemental Analysis Calculated (Found) C	H	N
1		169-170	$C_{14}H_{14}ClNO_2$	63.76 (63.68	5.35 5.20	5.31 5.33)
2		138-139	$C_{14}H_{14}ClNO_2$	63.76 (63.81	5.35 5.31	5.31 5.40)
3		123-125	$C_{15}H_{16}ClNO_2$	64.87 (64.64	5.81 5.77	5.04 5.03)
4		146-148	$C_{15}H_{16}ClNO_2$	64.87 (64.59	5.81 5.73	5.04 4.98)
5		142-144	$C_{15}H_{16}ClNO_2$	64.87 (64.90	5.81 5.76	5.04 5.01)

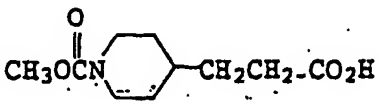
Table 52 (continued)

Comp. No.	Ar	Melting Point (°C)	Molecular Formula	Elemental Analysis Calculated (Found) C	H	N
6		127-129	$C_{18}H_{16}ClNO_2$	68.90 (68.93	5.14 5.04	4.46 4.37)
7		132-134	$C_{18}H_{16}ClNO_2$	68.90 (68.72	5.14 4.98	4.46 4.51)
8		136-138	$C_{17}H_{14}ClNO_3$	64.66 (64.61	4.47 4.49	4.43 4.32)

Reference Example 5

3-(1-Methoxycarbonyl-4-piperidinyl)propionic acid

[0090]



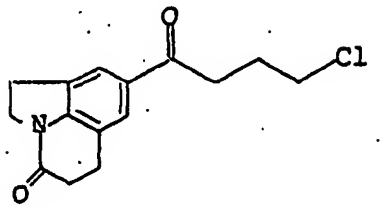
[0091] In 208 ml of conc. hydrochloric acid, 99.63 g of 3-(1-acetyl-4-piperidinyl)propionic acid was suspended; the suspension was stirred under refluxing conditions for six hours. The reaction mixture was then concentrated to half under reduced pressure and allowed to stand at 0°C overnight. The crystalline precipitate was collected by filtration and washed with cold ethanol. After drying, 77.9 g of 3-(4-piperidinyl)propionic acid was obtained. Of this product, 77.5 g was dissolved in a mixture of 360 ml of dichloromethane and 400 ml of 3N sodium hydroxide aqueous solution. To the mixture, 34 ml of methyl chlorocarbonate was added dropwise at 0°C, and stirred at room temperature for five hours. After the pH of the aqueous layer was adjusted to 8 by addition of a 50% sodium hydroxide aqueous solution, the organic layer was separated and dried over anhydrous sodium sulfate. The solvent was then evaporated under reduced pressure. To the residue, isopropyl ether-hexane was added to yield 76.5 g of the title compound as colorless crystals having a melting point of 88-90°C.

Elemental analysis (for $C_{10}H_{17}NO_4$)			
Calculated	C, 55.80;	H, 7.96;	N, 6.51
Found	C, 55.69;	H, 8.01;	N, 6.47

Reference Example 6

8-(4-Chlorobutylyl)-1,2,5,6-tetrahydro-4H-pyroro[3,2,1-ij]quinolin-4-one

[0092]



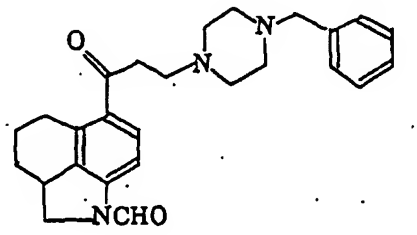
[0093] By the same procedure as used in Example 2, 5 g of 1,2,5,6-tetrahydro-4H-pyroro[3,2,1-ij]quinolin-4-one and 4.15 g of 4-chlorobutylyl chloride were reacted to yield 6.4 g of the title compound as colorless needles having a melting point of 130-131°C.

Elemental analysis (for $C_{15}H_{16}ClNO_2$)			
Calculated	C, 64.87;	H, 5.81;	N, 5.04
Found	C, 64.71;	H, 5.88;	N, 4.99

Example 1

1-(1-Formyl-1,2,2a,3,4,5-hexahydrobenz[cd]indol-6-yl)-3-[1-(phenylmethyl)piperazin-4-yl]-1-propanone

[0094]



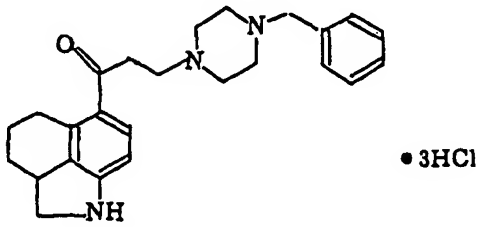
[0095] To a suspension of 0.65 g of 3-chloro-(1-formyl-1,2,2a,3,4,5-hexahydrobenz[cd]indol- 6-yl)-1-propanone as obtained in Reference Example 2 and 0.42 g of potassium carbonate in 20 ml of dichloromethane, a 5 ml solution of 0.41 g of 1-(phenylmethyl)piperazine in methanol was added, followed by stirring at room temperature for 30 minutes. After the solvent was distilled off under reduced pressure, water was added to the residue, and the reaction product was extracted with dichloromethane. After the extract was dried over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure. The resulting oily substance was purified by silica gel column chromatography (developing solvent: ethyl acetate-methanol = 10:1 (v/v)) to yield 0.6 g of the title compound as a colorless oily substance.

Elemental analysis (for $C_{26}H_{31}N_3O_2$):			
Calculated	C, 74.79;	H, 7.48;	N, 10.06
Found	C, 74.59;	H, 7.52;	N, 10.03

Example 2

1-(1,2,2a,3,4,5-Hexahydrobenz[cd]indol-6-yl)-3-[1-(phenylmethyl)piperazin-4-yl]-1-propanone trihydrochloride

[0096]



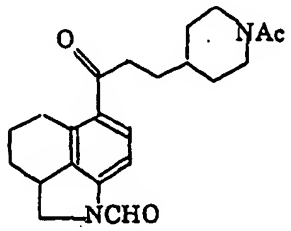
[0097] To a 10 ml solution of 0.4 g of 1-(1-formyl-1,2,2a,3,4,5-hexahydrobenz[cd]indol-6-yl)-3-[1-(phenylmethyl)piperazin-4-yl]-1-propanone as obtained in Example 1 in methanol, 10 ml of 3 N hydrochloric acid was added, followed by stirring at room temperature for 30 minutes. After the methanol was distilled off under reduced pressure, a 10% aqueous sodium hydroxide solution was added to obtain a solution pH of about 10, and the reaction product was extracted with dichloromethane. After the product was dried over anhydrous sodium sulfate, 0.8 ml of 4 N methanol-hydrochloric acid was added. The solvent was distilled off under reduced pressure, and the resulting solid was crystallized from methanol-ether to yield 0.46 g of the title compound as a colorless crystal having a melting point of 207 to 211°C (decomposed).

Elemental analysis (for $C_{25}H_{31}N_3O \cdot 3HCl$):			
Calculated	C, 60.18;	H, 6.87;	N, 8.42
Found	C, 59.98;	H, 7.01;	N, 8.22

Example 3

3-(1-Acetylpiperidin-4-yl)-1-(1-formyl-1,2,2a,3,4,5-hexahydrobenz[cd]indol-6-yl)-1-propanone

[0098]



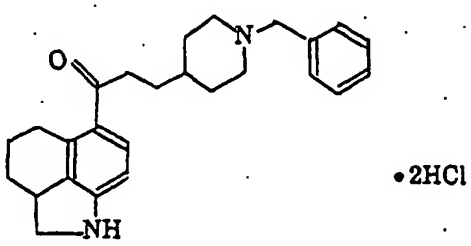
[0099] To a 10 ml solution of 0.8 g of 1-formyl-1,2,2a,3,4,5-hexahydrobenz[cd]indole as obtained in Reference Example 1 and 1.2 g of 3-(1-acetylpiperidin-4-yl)propionyl chloride in 1,2-dichloroethane, 2.0 g of aluminum chloride was added portionwise, followed by heating and refluxing for 2 hours. The reaction mixture was poured over ice water, and the reaction product was extracted with dichloromethane. After the extract was dried over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure. The resulting residue was purified by silica gel column chromatography (developing solvent: ethyl acetate-methanol = 20:1 (v/v)) to yield 1.0 g of the title compound as a viscous oily substance.

Elemental analysis (for $C_{22}H_{28}N_2O_3$):			
Calculated	C, 71.71;	H, 7.66;	N, 7.60
Found	C, 71.47;	H, 7.58;	N, 7.57

Example 4

1-(1,2,2a,3,4,5-Hexahydrobenz[cd]indol-6-yl)-3-[1-(phenylmethyl) piperidin-4-yl]-1-propanone dihydrochloride

[0100]



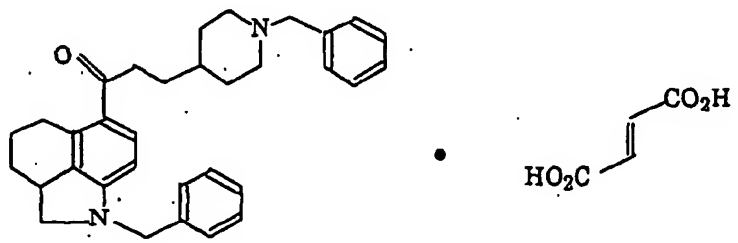
[0101] A mixture of 0.4 g of 3-(1-acetylpiperidin-4-yl)-1-(1-formyl-1,2,2a,3,4,5-hexahydrobenz[cd]indol-6-yl)-1-propanone as obtained in Example 3 and 10 ml of concentrated hydrochloric acid was heated and refluxed for 8 hours. After the concentrate hydrochloric acid was distilled off under reduced pressure, the residue was dissolved in water, and a 10% aqueous sodium hydroxide solution was added to obtain a solution pH of about 11. The reaction product was extracted with dichloromethane. After the product was dried over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure. The resulting oily substance was dissolved in 10 ml of ethanol, after which 0.2 g of potassium carbonate was added, followed by drop by drop addition of a 2 ml ethanol solution of 0.17 g of benzyl bromide. After the mixture was stirred at room temperature for 1 hour, the solvent was distilled off under reduced pressure. After water was added to the residue, the reaction product was extracted with dichloromethane. After the extract was dried over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure. The resulting oily substance was purified by silica gel column chromatography (developing solvent: dichloromethane-ethyl acetate = 2:1 (v/v)) to yield a free base form of the title compound as a colorless oily substance. After 0.6 ml of 4 N methanol-hydrochloric acid was added to the oily substance, the solvent was distilled off, to yield 0.36 g of the title compound as an amorphous powder.

Elemental analysis (for $C_{26}H_{32}N_2O \cdot 2HCl$):			
Calculated	C, 67.67;	H, 7.43;	N, 6.07
Found	C, 67.43;	H, 7.44;	N, 6.02

Example 5

1-[1-(Phenylmethyl)-1,2,2a,3,4,5-hexahydrobenz[cd]indol-6-yl]-3-[1-(phenylmethyl)piperidin-4-yl]-1-propanone fumarate

[0102]



[0103] To a 10 ml solution of 0.5 g of 1-(1,2,2a,3,4,5-hexahydrobenz[cd]indol-6-yl)-3-[1-(phenylmethyl)piperidin-4-yl]-1-propanone in ethanol, 0.23 g of potassium carbonate was added, followed by dropwise addition of a 2 ml ethanol solution of 0.22 g of benzyl bromide. After the mixture was stirred at room temperature for 1 hour, the solvent was distilled off under reduced pressure. After water was added to the residue, the reaction product was extracted with

dichloromethane. After the extract was dried over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure. The resulting oily substance was purified by silica gel column chromatography (developing solvent: ethyl acetate-methanol = 40:1 (v/v)) to yield 0.47 g of a free base form of the title compound as a colorless crystal having a melting point of 143 to 146°C.

Elemental analysis (for $C_{33}H_{38}N_2O$):			
Calculated	C, 82.80;	H, 8.00;	N, 5.85
Found	C, 82.71;	H, 8.02;	N, 5.74

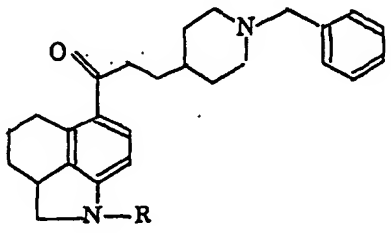
[0104] To a 5 ml solution of the resulting crystal in dichloromethane, a solution of 114 mg of fumaric acid in 5 ml of methanol was added, after which the solvent was distilled off under reduced pressure, to yield 0.53 g of the title compound as a colorless crystal having a melting point of 164 to 166°C.

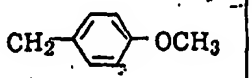
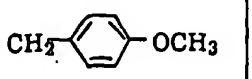
Elemental analysis (for $C_{33}H_{38}N_2O \cdot C_4H_4O_4 \cdot 1/2H_2O$):			
Calculated	C, 73.61;	H, 7.18;	N, 4.64
Found	C, 73.43;	H, 7.04;	N, 4.71

Example 6

[0105] The same procedure as in Example 6 was followed to yield the compounds listed in Table 53.

Table 53

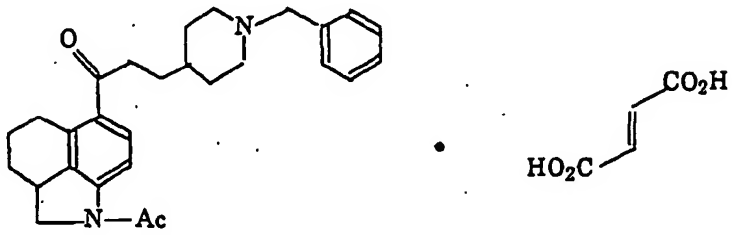


Compound No.	R	Melting Point (°C)	Molecular Formula	Elemental Analysis Calculated (Found)		
				C	H	N
1		115-117	$C_{34}H_{40}N_2O_2$	80.28 (80.11	7.93 7.96	5.51 5.38)
2		110-114	$C_{34}H_{40}N_2O_2 \cdot C_4H_4O_4$	73.05 (72.93	7.10 7.15	4.48 4.31)

Example 7

1-(1-Acetyl-1,2,2a,3,4,5-hexahydrobenz[cd]indol-6-yl)-3-[1-(phenylmethyl)piperidin-4-yl]-1-propanone fumarate

[0106]



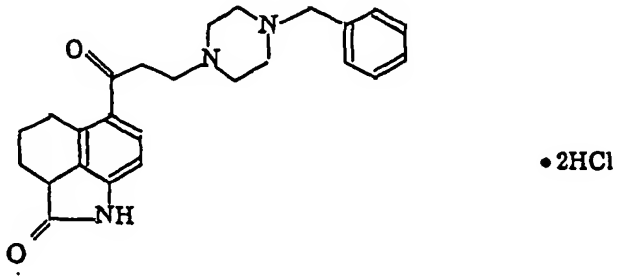
[0107] To a 10 ml solution of 0.5 g of 1-(1,2,2a,3,4,5-hexahydrobenz[cd]indol-6-yl)-3-[1-(phenylmethyl)piperidin-4-yl]-1-propanone in dichloromethane, 0.14 g of acetic anhydride was added, followed by stirring at room temperature for 30 minutes. After 20 ml of a 5% aqueous sodium hydroxide solution was added to the reaction mixture, the reaction product was extracted with dichloromethane. After the extract was dried over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (developing solvent: ethyl acetate-methanol = 20:1 (v/v)) to yield 0.48 g of a free base form of the title compound as a colorless powder. To a 5 ml solution of the resulting powder in dichloromethane, a 5 ml solution of 0.13 g of fumaric acid in methanol was added, after which the solvent was distilled off under reduced pressure, to yield 0.54 g of the title compound as a colorless crystal having a melting point of 173 to 175°C.

Elemental analysis (for $C_{28}H_{34}N_2O_2 \cdot C_4H_4O_4$):			
Calculated	C, 70.31;	H, 7.01;	N, 5.12
Found	C, 70.11;	H, 7.16;	N, 5.13

Example 8

1-(2-Oxo-2a,3,4,5-tetrahydro-1H-benz[cd]indol-6-yl)-3-[4-(phenylmethyl)piperazin-1-yl]-1-propanone dihydrochloride

[0108]



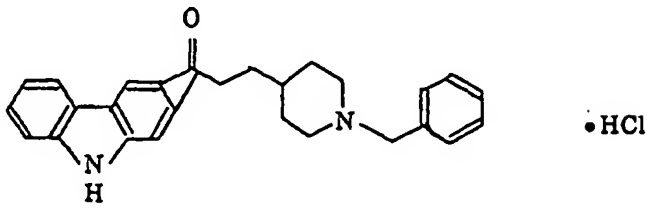
[0109] Using the compound obtained in Reference Example 4, the same procedure as in Example 1 was followed to yield a free base form of the title compound, which was converted to a dihydrochloride by the method described in Example 2 to yield the title compound as a colorless crystal having a melting point of 185 to 188°C.

Elemental analysis (for $C_{25}H_{29}N_3O_2 \cdot 2HCl$):			
Calculated	C, 63.02;	H, 6.56;	N, 8.82
Found	C, 62.88;	H, 6.57;	N, 8.75

Reference Example 8 (not claimed)

1-(3-Carbazolyl)-3-[1-(phenylmethyl)piperidin-4-yl]-1-propanone hydrochloride

[0110]



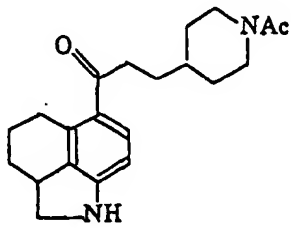
[0111] To a solution of 0.7 g of 1-(3-carbazolyl)-3-(piperidin-4-yl)-1-propane as obtained in Example 12 in a mixture of N,N-dimethylformamide-dichloromethane (3/1 (v/v)), 0.41 g of potassium carbonate was added, followed by stirring at 15°C for 15 minutes. Then, a solution of 0.37 g of benzyl bromide in 3 ml of dichloromethane was added dropwise, followed by stirring at room temperature for 2.5 hours. After the solvent was distilled off, 30 ml of distilled water and 30 ml of dichloromethane were added, and the organic layer was separated, washed with 50 ml of distilled water and then dried over anhydrous sodium sulfate. The solvent was distilled off to yield a crystal, which was dried under reduced pressure to yield 0.69 g of a free base form of the title compound as a colorless crystal having a melting point of 155 to 158°C. A 0.55 g portion of this free base form was dissolved in methanol, and 0.5 ml of 4 N methanol-hydrochloric acid was added, after which the solvent was distilled off under reduced pressure, to yield a solid, which was washed with ethanol, to yield 0.52 g of the title compound as a light blue crystal having a melting point of 206 to 208°C.

Elemental analysis (for $C_{27}H_{28}N_2O \cdot HCl \cdot 1/2H_2O$):			
Calculated	C, 73.37;	H, 6.84;	N, 6.34
Found	C, 73.46;	H, 6.77;	N, 6.46

Example 9

3-(1-Acetylpiperidin-4-yl)-1-(1,2,2a,3,4,5-hexahydrobenz[cd]indol-6-yl)-1-propanone

[0112]



1) Using 17 g of 1-formyl-1,2,2a,3,4,5-hexahydrobenz[cd]indole (compound of Reference Example 1), the same procedure as in Example 3 was followed to yield 20 g of 3-(1-acetylpiperidin-4-yl)-1-(1-formyl-1,2,2a,3,4,5-hexahydrobenz[cd]indol-6-yl)-1-propanone.

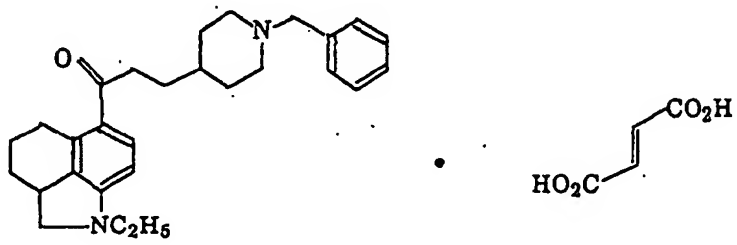
2) A mixture of a 150 ml methanol solution of 20 g of the compound obtained in 1) above and 150 ml of 10% hydrochloric acid was stirred at room temperature for 30 minutes. After the methanol was distilled off under reduced pressure, a 10% aqueous sodium hydroxide solution was added to obtain a solution pH of about 10. The reaction product was extracted with dichloromethane. After the product was dried over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure to yield a 17 g crude crystal of the title compound, which was recrystallized from dichloromethaneether to yield a 9.8 g colorless crystal having a melting point of 167 to 169°C.

Elemental analysis (for $C_{21}H_{28}N_2O_2$):			
Calculated	C, 74.08;	H, 8.29;	N, 8.23
Found	C, 73.79;	H, 8.33;	N, 8.12

Example 10

1-(1-Ethyl-1,2,2a,3,4,5-hexahydrobenz[cd]indol-6-yl)-3-[1-(phenylmethyl)piperidin-4-yl]-1-propanone fumarate

[0113]



1) A 10 ml suspension of 1.0 g of 3-(1-acetylpiperidin-4-yl)-1-(1,2,2a,3,4,5-hexahydrobenz[cd]indol-6-yl)-1-propanone, 2.3 g of ethyl iodide and 0.53 g of potassium carbonate in ethanol was stirred at 60 to 70°C for 12 hours. After the solvent was distilled off under reduced pressure, water was added to the residue, after which the reaction product was extracted with dichloromethane. After the extract was dried over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (developing solvent: ethyl acetate) to yield 0.82 g of 3-(1-acetylpiperidin-4-yl)-1-(1-ethyl-1,2,2a,3,4,5-hexahydrobenz[cd]indol-6-yl)-1-propanone as a colorless oily substance.

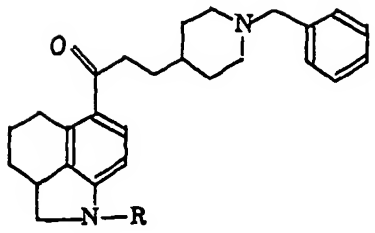
Elemental analysis (for $C_{23}H_{32}N_2O_2$):			
Calculated	C, 74.96;	H, 8.75;	N, 7.60
Found	C, 74.88;	H, 8.74;	N, 7.62

2) Using 0.75 g of the compound obtained in 1) above, the same procedure as in Example 4 was followed to yield 0.65 g of a free base form of the title compound. To a 5 ml solution of the resulting 0.65 g of free base form in dichloromethane, a 5 ml solution of 0.18 g of fumaric acid in methanol was added, after which the solvent was distilled off under reduced pressure, to yield a crystal, which was recrystallized from ethanol, to yield 0.68 g of the title compound as a colorless crystal having a melting point of 177 to 178°C.

Elemental analysis (for $C_{28}H_{36}N_2O \cdot C_4H_4O_4 \cdot 3/2H_2O$):			
Calculated	C, 68.67;	H, 7.74;	N, 5.01
Found	C, 69.05;	H, 7.50;	N, 5.26

Example 11

[0114] Using the compound obtained in Example 9, the same procedure as in Example 10 was followed to yield the compounds listed in the following Table 2

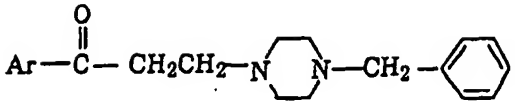


Comp. No.	R	Melting Point (°C)	Molecular Formula	Elemental Analysis Calculated (Found)		
				C	H	N
1	CH_3	160-162	$C_{27}H_{34}N_2O \cdot C_4H_4O_4 \cdot 1/2H_2O$	70.56 (70.46	7.45 7.27	5.31 5.44)
2	$(CH2)_2CH_3$	200-204	$C_{29}H_{38}N_2O \cdot C_4H_4O_4$	72.50 (72.24	7.74 7.73	5.12 5.27)
3	$CH(CH_3)_2$	149-153	$C_{29}H_{38}N_2O \cdot C_4H_4O_4$	72.50 (72.47	7.74 7.67	5.12 5.28)
4	$(CH_2)_3CH_3$	189-193	$C_{30}H_{40}N_2O \cdot C_4H_4O_4 \cdot 1/4H_2O$	72.25 (72.19	7.94 7.91	4.96 5.19)
5	$CH_2CH(CH_3)_2$	180-181	$C_{30}H_{40}N_2O \cdot C_4H_4O_4$	72.83 (72.64	7.91 7.87	5.00 4.76)
6	$(CH_2)_4CH_3$	179-181	$C_{31}H_{42}N_2O \cdot C_4H_4O_4 \cdot 1/4H_2O$	72.57 (72.64	8.09 8.03	4.84 5.07)

Example 12

[0115] Using the compound obtained in Reference Example 5, the same procedure as in Example 1 was followed to yield the compounds listed in Table 3.

Table 3



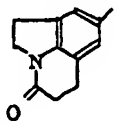
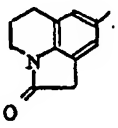
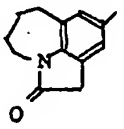
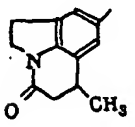
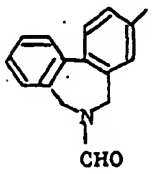
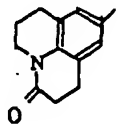
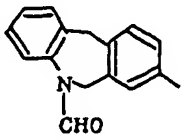
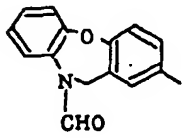
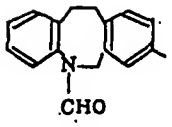
Comp. No.	Ar	Melting Point (°C)	Molecular Formula	Elemental Analysis Calculated (Found) C	H	N
1		246-248	$C_{25}H_{29}N_3O_2 \cdot 2HCl$	63.02 (62.78	6.56 6.60	8.82 8.77)
2		224-227 (decomp.)	$C_{25}H_{29}N_3O_2 \cdot 2HCl \cdot 1/2H_2O$	61.85 (61.57	6.64 6.47	8.66 8.36)
3		224-228 (decomp.)	$C_{26}H_{31}N_3O_2 \cdot 2HCl \cdot H_2O$	61.41 (61.36	6.94 6.69	8.26 8.26)
4		227-230	$C_{26}H_{31}N_3O_2 \cdot 2HCl \cdot 1/2H_2O$	62.52 (62.77	6.86 6.68	8.41 8.45)
5		168-172 (decomp.)	$C_{29}H_{31}N_3O_2 \cdot 2HCl \cdot 3H_2O$	60.00 (59.78	6.77 6.82	7.24 7.27)

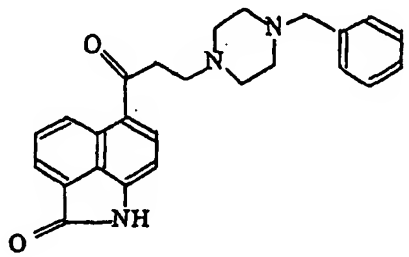
Table 3 (continued)

Comp. No.	Ar	Melting Point (°C)	Molecular Formula	Elemental Analysis Calculated (Found) C	H	N
6		240-242	$C_{26}H_{31}N_3O_2 \cdot 2HCl \cdot H_2O$	61.41 (61.35	6.94 6.82	8.26 8.29)
7		197-200	$C_{29}H_{31}N_3O_2 \cdot 2HCl$	66.15 (65.91	6.32 6.42	7.98 7.93)
8		188-191	$C_{28}H_{29}N_3O_3 \cdot 2HCl \cdot 1/2H_2O$	62.57 (62.87	6.00 5.88	7.82 7.85)
9		188-191	$C_{30}H_{33}N_3O_2 \cdot 2HCl \cdot H_2O$	64.51 (64.69	6.68 6.74	7.52 7.62)

Reference Example 7 (not claimed)

1-(2-Oxo-1H-benz[cd]indol-6-yl)-3-[4-(phenylmethyl)piperazin-1-yl]-1-propanone dihydrochloride

[0116]



• 2HCl

1) Using 7.5 g of benz[cd]indol-2(1H)-one and 6.2 g of 3-chloropropionyl chloride, the same procedure as in Reference Example 2 was followed to yield 4.8 g of an about 1:1 mixture of 3-chloro-1-(2-oxo-1H-benz[cd]indol-6-yl)-1-propanone and unreacted benz[cd]indol-2(1H)-one.

2) To a solution of 1.0 g of the mixture obtained in 1) above in a mixture of dimethylformamide-dichloromethane

(2 ml/20 ml), 0.68 g of 1-benzylpiperazine and 0.34 g of potassium carbonate were added, followed by stirring at room temperature for 1 hour. After the solvent was distilled off under reduced pressure, water was added to the residue, after which the reaction product was extracted with dichloromethane. After the extract was dried over anhydrous sodium sulfate, the solvent was distilled off. The residue was purified by silica gel column chromatography [developing solvent: ethyl acetate-methanol = 10:1 (v/v)] to yield a fraction containing the desired product. The solvent was distilled off under reduced pressure to yield 0.52 g of a free base form of the title compound as a colorless powder having a melting point of 208 to 210°C, which was then converted to a dihydrochloride by the method described in Example 2 to yield 0.51 g of the title compound as a colorless crystal having a melting point of 166 to 170°C.

Elemental analysis (for $C_{25}H_{26}N_3O_2 \cdot 2HCl \cdot 3/2H_2O$):			
Calculated	C, 60.12;	H, 6.05;	N, 8.41
Found	C, 60.17;	H, 6.25;	N, 8.19

Example 13

[0117] The same procedure as in Reference Example 7 was followed to yield the compound listed in Table 4.

Table 4

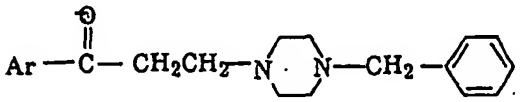
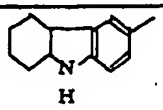


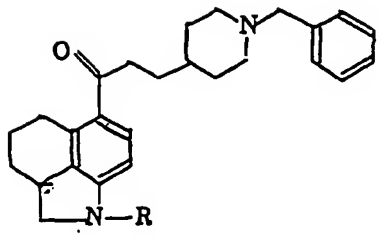
Table 4

Compound No.	R	Melting Point (°C)	Molecular Formula	Elemental Analysis Calculated (Found) C	H	N
1		165-167	$C_{26}H_{33}N_3O \cdot 2C_4H_4O_4$	64.24 (64.07	6.50 6.57	6.61 6.40)

Example 14

[0118] Using1-(1,2,2a,3,4,5-hexahydrobenz[cd]indol-6-yl)-3-[1-(phenylmethyl)piperizin-4-yl]-1-propanone as obtained in Example 4, the same procedure as in Example 7 was followed to yield the compounds listed in Table 5.

Table 5

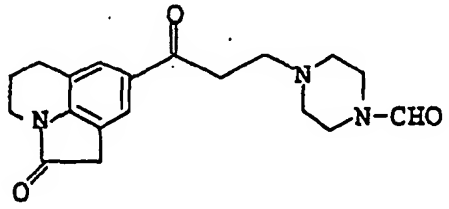


Comp. No.	R	Melting Point (°C)	Molecular Formula	Elemental Analysis Calculated (Found) C	H	N
1	$COCH_2CH_3$	140-142	$C_{29}H_{36}N_2O_2 \cdot C_4H_4O_4$	70.69 (70.46	7.19 7.21	5.00 4.97)
2	COPh	Amorphous	$C_{33}H_{36}N_2O_2 \cdot C_4H_4O_4$	73.00 (72.95	6.62 6.64	4.60 4.53)

Example 15

8-[3-(4-Formyl-1-piperazinyl)-1-oxopropyl]-5,6-dihydro-4H-pyroro[3,2,1-ij]quinolin-2(1H)-one

[0119]



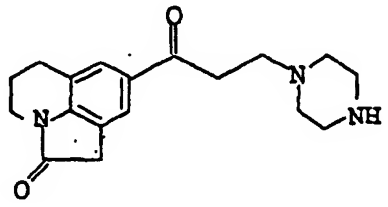
[0120] By the same procedure as used in Example 1, 13.8 g of 8-(3-chloropropyonyl)-5,6-dihydro-4H-pyroro[3,2,1-ij] quinolin-2(1H)-one described as compound 2 in Reference Example 6, and 7.8 g of 1-piperazine-carboxyaldehyde were reacted to yield 11.0 g of the title compound as a colorless powder having a melting point of 143-147°C.

Elemental analysis (for $C_{19}H_{23}N_3O_3$)			
Calculated	C, 66.84;	H, 6.79;	N, 12.31
Found	C, 66.69;	H, 6.79;	N, 12.07

Example 16

8-[3-(1-Piperazinyl)-1-oxopropyl]-5,6-dihydro-4H-pyroro[3,2,1-ij]quinolin-2(1H)-one

[0121]



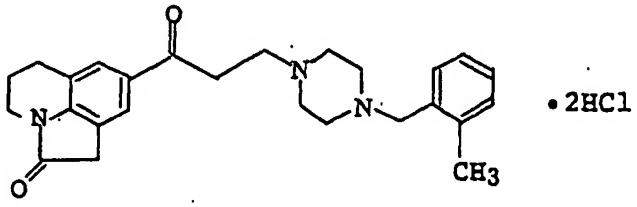
[0122] To 30 ml of methanol containing 9.0 g of 8-[3-(4-formyl-1-piperazinyl)-1-oxopropyl]-5,6-dihydro-4H-pyroro [3,2,1-ij]quinolin-2(1H)-one obtained in Example 21, 10 ml of conc. hydrochloric acid was added and stirred at room temperature for 14 hours. The solvent was evaporated under reduced pressure. The residual aqueous solution was washed with ethyl acetate, and adjusted to about pH 11 by addition of a sodium hydroxide aqueous solution for extraction with dichloromethane. The extract was dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure to yield 6.3 g of the title compound as an amorphous powder.

Elemental analysis (for $C_{18}H_{23}N_3O_2$)			
Calculated	C, 68.98;	H, 7.40;	N, 13.41
Found	C, 69.02;	H, 7.38;	N, 13.25

Example 17

8-[3-[4-[(2-Methylphenyl)methyl]-1-piperazinyl]-1-oxopropyl]-5,6-dihydro-4H-pyroro[3,2,1-ij]quinolin-2(1H)-one dihydrochloride

[0123]



[0124] In 10 ml of dichloromethane, 0.34 g of 8-[3-(1-piperazinyl)-1-oxopropyl]-5,6-dihydro-4H-pyroro[3,2,1-ij]quinolin-2(1H)-one obtained in Example 22 and 0.19 mg of 2-methylbenzyl bromide were suspended; the suspension was stirred at room temperature for six hours. After evaporation of the solvent, the residue was dissolved in a 10% hydrochloric acid aqueous solution and washed with ethyl acetate. The aqueous phase was adjusted to pH 11 by addition of a sodium hydroxide aqueous solution for extraction with dichloromethane. The extract was dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was then purified by silica gel column chromatography (developing solvent: ethyl acetate-methanol = 10 : 1 (v/v)) to yield 0.32 g of the colorless oily title compound in a free form. To this oily substance, 0.5 ml of 4N methanolic hydrochloric acid was added, followed by evaporation of the solvent. The title compound (as dihydrochloride) was thus obtained, in a yield of 0.34 g, as colorless crystals having a melting point of 205-208°C.

Elemental analysis (for $C_{26}H_{31}N_3O_2 \cdot 2HCl \cdot H_2O$)			
Calculated	C, 61.41;	H, 6.94;	N, 8.26

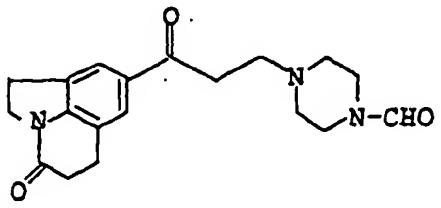
(continued)

Elemental analysis (for $C_{26}H_{31}N_3O_2 \cdot 2HCl \cdot H_2O$)			
Found	C, 61.64;	H, 6.76;	N, 8.25

Example 18

8-[3-(4-Formyl-1-piperazinyl)-1-oxopropyl]-1,2,5,6-tetrahydro-4H-pyroro[3,2,1-ij]quinolin-4-one

[0125]



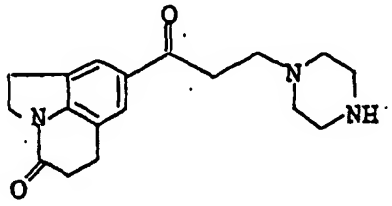
[0126] By the same procedure as used in Example 1, 20.0 g of 8-(3-chloropropionyl)-1,2,5,6-tetrahydro-4H-pyroro [3,2,1-ij]quinolin-4-one, described as compound 1 in Example 6, and 11.4 g of 1-piperazine carboxyaldehyde were reacted to yield 20.4 g of the title compound as a colorless powder.

Elemental analysis (for $C_{19}H_{23}N_3O_3$)			
Calculated	C, 66.84;	H, 6.79;	N, 12.31
Found	C, 66.79;	H, 6.58;	N, 12.05

Example 19

8-[3-(1-Piperazinyl]-1-oxopropyl]-1,2,5,6-tetrahydro-4H-pyroro[3,2,1-ij]quinolin-4-one

[0127]



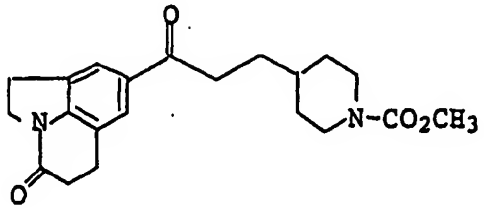
[0128] Of 8-[3-(4-formyl-1-piperazinyl]-1-oxopropyl]-1,2,5,6-tetrahydro-4H-pyroro[3,2,1-ij]quinolin-4-one obtained in Example 24, 20 g was reacted by the same procedure as used in Example 22 to yield 14.0 g of the title compound as a colorless powder.

Elemental analysis (for $C_{18}H_{23}N_3O_2$)			
Calculated	C, 68.98;	H, 7.40;	N, 13.41
Found	C, 68.69;	H, 7.29;	N, 13.27

Example 20

8-[3-(1-Methoxycarbonyl-4-piperidinyl)-1-oxopropyl]-1,2,5,6-tetrahydro-4H-pyroro[3,2,1-ij]quinolin-4-one

[0129]



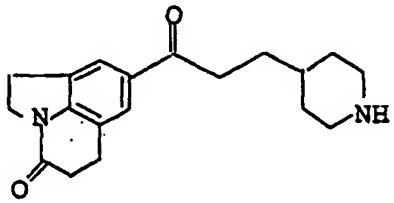
[0130] To 109 ml of thionyl chloride, 65.6 g of 3-(1-methoxycarbonyl-4-piperidinyl)propionic acid obtained in Example 7 was added in small portions at 0-5°C. The obtained solution was stirred at 0-5°C for 20 minutes. After the thionyl chloride was evaporated under reduced pressure, the residue and 43.3 g of 1,2,5,6-tetrahydro-4H-pyroro[3,2,1-ij]quinolin-4-one were reacted by the same procedure as in Example 2 to yield 34.0 g of the title compound as colorless crystals having a melting point of 139-140°C.

Elemental analysis (for $C_{21}H_{26}N_2O_4$)			
Calculated	C, 68.09;	H, 7.07;	N, 7.56
Found	C, 68.21;	H, 7.01;	N, 7.29

Example 21

8-[3-(4-Piperidinyl)-1-oxopropyl]- 1,2,5,6-tetrahydro-4H-pyroro[3,2,1-ij]quinolin-4-one

[0131]



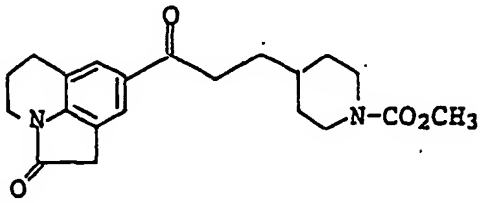
[0132] In a mixture of 200 ml of methanol and 400 ml of conc. hydrochloric acid, 34.0 g of 8-[3-(1-methoxycarbonyl-4-piperidinyl)-1-oxopropyl]-1,2,5,6-tetrahydro-4H-pyroro[3,2,1-lj]quinolin-4-one obtained in Example 26 was dissolved; the solution was stirred for 16 hours under refluxing conditions. After cooling, the methanol was evaporated under reduced pressure. The residue, adjusted to pH 8-9 by addition of a 50% sodium hydroxide aqueous solution, was extracted twice with 500 ml of dichloromethane each time. The extracts were dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The obtained residue was crystallized from diethyl ether-ethyl acetate to yield 28.3 g of the title compound as colorless crystals having a melting point of 114-116°C.

Elemental analysis (for $C_{19}H_{24}N_2O_2$)			
Calculated	C, 73.05;	H, 7.74;	N, 8.97
Found	C, 73.21;	H, 7.65;	N, 8.99

Example 22

8-[3-(1-Methoxycarbonyl-4-piperidinyl)-1-oxopropyl]-5,6-dihydro-4H-pyroro[3,2,1-ij]quinolin-2(1H)-one

[0133]



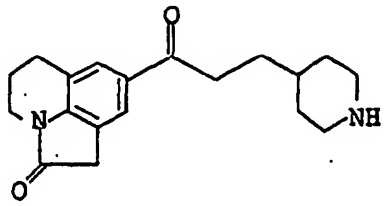
[0134] By the same procedure as in Example 20, 3-(1-methoxycarbonyl-4-piperidinyl)propionic acid obtained in Example 6 and well-known 5,6-dihydro-4H-pyroro[3,2,1-ij]quinolin-2(1H)-one were reacted to yield the title compound as colorless crystals having a melting point of 140-141°C.

Elemental analysis (for $C_{21}H_{26}N_2O_4$)			
Calculated	C, 68.09;	H, 7.07;	N, 7.56
Found	C, 68.00;	H, 7.12;	N, 7.73

Example 23

8-[3-(4-Piperidinyl)-1-oxopropyl]-5,6-dihydro-4H-pyroro[3,2,1-ij]quinolin-2(1H)-one

[0135]



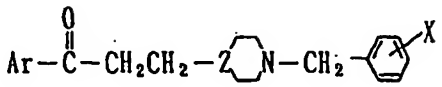
[0136] By the same procedure as in Example 21, 8-[3-(1-methoxycarbonyl-4-piperidinyl)-1-oxopropyl]-5,6-dihydro-4H-pyroro[3,2,1-ij]quinolin-2(1H)-one obtained in Example 22 was reacted to yield the title compound as a colorless oily substance.

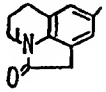
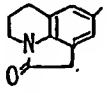
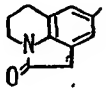
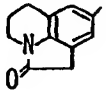
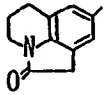
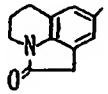
Elemental analysis (for $C_{19}H_{24}N_2O_2$)			
Calculated	C, 73.05;	H, 7.74;	N, 8.97
Found	C, 73.10;	H, 7.58;	N, 8.73

Example 24

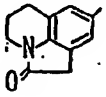
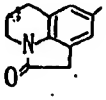
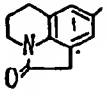
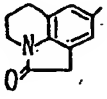
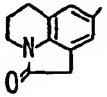
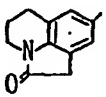
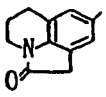
[0137] Using the compound as obtained in Example 16 or 19, the same procedure as in Example 17 was followed to yield the compounds listed in Table 5 compounds 1-36, 66-71 (method A). Using the compound as obtained in Example 21 or 23, the same procedure as in Reference Example 8 was followed to yield the compounds listed in Table 5 compounds 37-65, 72-76 (method B).

[Table 5]

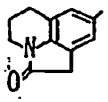
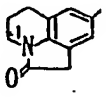
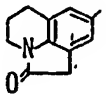
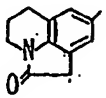
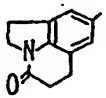
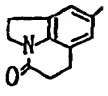
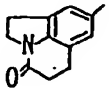


Comp. No.	Method	Ar	Z	X	m.p. (℃)	Molecular Formula	Elemental Analysis Calcd. (Found) C	H	N
1	A		N	3-CH_3	210-214	$C_{26}H_{31}N_3O_2$	61.41	6.94	8.26
						$\cdot 2HCl \cdot H_2O$	(61.63	6.83	8.43)
2	A		N	4-CH_3	216-218	$C_{26}H_{31}N_3O_2$	62.52	6.86	8.41
						$\cdot 2HCl \cdot 1/2H_2O$	(62.25	6.66	8.12)
3	A		N	2-Cl	218-220	$C_{25}H_{28}ClN_3O_2$	54.90	6.27	7.68
						$\cdot 2HCl \cdot 2H_2O$	(55.08	6.20	7.56)
4	A		N	3-Cl	215-217	$C_{25}H_{28}ClN_3O_2$	56.77	6.10	7.94
						$\cdot 2HCl \cdot H_2O$	(56.73	5.97	7.87)
5	A		N	4-Cl	209-213	$C_{25}H_{28}ClN_3O_2$	56.77	6.10	7.94
						$\cdot 2HCl \cdot H_2O$	(57.07	5.94	7.69)
6	A		N	2-C_2H_5	217-220	$C_{27}H_{33}N_3O_2$	62.06	7.14	8.04
						$\cdot 2HCl \cdot H_2O$	(62.16	6.91	8.00)

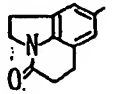
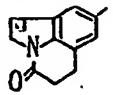
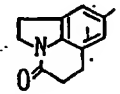
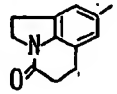
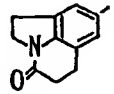
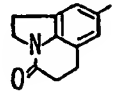
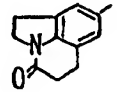
[Table 5, continued]

Comp. No.	Method	Ar	Z	X	m.p. (℃)	Molecular Formula	Elemental Analysis Calcd. (Found) C	H	N
7	A		N	4−C_2H_5	205−209	$C_{27}H_{33}N_3O_2$	62.06	7.14	8.04
						·2HCl·H_2O	(62.30	7.01	8.22)
8	A		N	3.4−$(CH_3)_2$	207−209	$C_{27}H_{33}N_3O_2$	62.06	7.14	8.04
						·2HCl·H_2O	(61.85	6.92	7.90)
9	A		N	2.5−$(CH_3)_2$	185-190	$C_{27}H_{33}N_3O_2$	62.06	7.14	8.04
						·2HCl·H_2O	(62.14	7.05	7.92)
10	A		N	2−F	215−217	$C_{25}H_{28}FN_3O_2$	59.64	6.21	8.35
						·2HCl·1/2H_2O	(59.41	6.23	8.06)
11	A		N	3−F	228−230	$C_{25}H_{28}FN_3O_2$	59.64	6.21	8.35
						·2HCl·1/2H_2O	(59.85	6.11	8.23)
12	A		N	4−F	220−223	$C_{25}H_{28}FN_3O_2$	59.64	6.21	8.35
						·2HCl·1/2H_2O	(59.45	6.10	8.11)
13	A		N	2−OCH_3	222−225	$C_{26}H_{31}N_3O_3$	58.54	6.80	7.88
						·2HCl·3/2H_2O	(58.35	6.54	7.66)

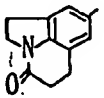
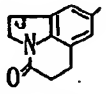
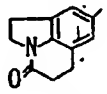
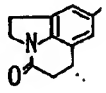
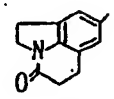
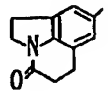
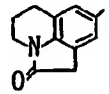
[Table 5, continued]

Comp. No.	Method	Ar	Z	X	m.p. (℃)	Molecular Formula	Elemental Analysis Calcd. (Found) C	H	N
14	A		N	3−OCH_3	203−207	$C_{26}H_{31}N_3O_3$	59.54	6.73	8.01
						·2HCl·H_2O	(59.69	6.66	7.89)
15	A		N	4−OCH_3	209−212	$C_{26}H_{31}N_3O_3$	60.58	6.65	8.15
						·2HCl·1/2H_2O	(60.38	6.47	7.99)
16	A		N	2−OH	188−190	$C_{25}H_{29}N_3O_3$	58.82	6.52	8.23
						·2HCl·H_2O	(58.97	6.62	8.04)
17	A		N	4−OCH_2Ph	134−138	$C_{32}H_{35}N_3O_3$	75.41	6.92	8.25
							(75.37	6.99	7.98)
18	A		N	2−CH_3	220−222	$C_{26}H_{31}N_3O_2$	55.51	7.35	7.47
						·2HCl·4H_2O	(55.31	7.10	7.28)
19	A		N	3−CH_3	232−238	$C_{26}H_{31}N_3O_2$	62.52	6.86	8.41
						·2HCl·1/2H_2O	(62.25	6.71	8.21)
20	A		N	4−CH_3	243−244	$C_{26}H_{31}N_3O_2$	61.41	6.94	8.26
						·2HCl·H_2O	(61.36	6.84	8.07)

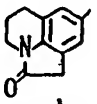
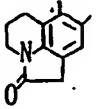
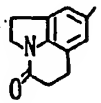
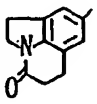
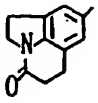
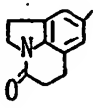
[Table 5, continued]

Comp. No.	Method	Ar	Z	X	m.p. (℃)	Molecular Formula	Elemental Analysis Calcd. (Found) C	H	N
21	A		N	2-Cl	226-230	$C_{25}H_{28}ClN_3O_2$	54.01	6.35	7.56
						$\cdot 2HCl \cdot 5/2H_2O$	(53.88	6.09	7.51)
22	A		N	3-Cl	227-234	$C_{25}H_{28}ClN_3O_2$	57.76	6.01	8.08
						$\cdot 2HCl \cdot 1/2H_2O$	(57.87	6.23	7.85)
23	A		N	4-Cl	228-231	$C_{25}H_{28}ClN_3O_2$	55.82	6.18	7.81
						$\cdot 2HCl \cdot 3/2H_2O$	(55.96	5.91	8.01)
24	A		N	2-F	232-233	$C_{25}H_{28}FN_3O_2$	58.60	6.29	8.20
						$\cdot 2HCl \cdot H_2O$	(58.48	6.20	8.04)
25	A		N	3-F	234-238	$C_{25}H_{28}FN_3O_2$	59.64	6.21	8.35
						$\cdot 2HCl \cdot 1/2H_2O$	(59.72	6.09	8.39)
26	A		N	4-F	228-232	$C_{25}H_{28}FN_3O_2$	58.60	6.29	8.20
						$\cdot 2HCl \cdot H_2O$	(58.72	6.04	8.00)
27	A		N	2.5-$(CH_3)_2$	223-225	$C_{27}H_{33}N_3O_2$	63.15	7.07	8.18
						$\cdot 2HCl \cdot 1/2H_2O$	(62.97	6.89	7.97)

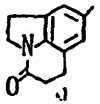
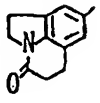
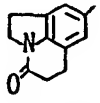
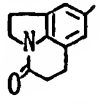
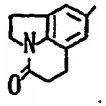
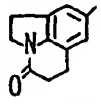
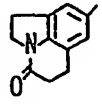
[Table 5, continued]

Comp. No.	Method	Ar	Z	X	m.p. (℃)	Molecular Formula	Elemental Analysis Calcd. (Found) C	H	N
28	A		N	3,4-$(CH_3)_2$	244-246	$C_{27}H_{33}N_3O_2$	63.15	7.07	8.18
						·2HCl·1/2H_2O	(62.99	7.04	7.93)
29	A		N	3-NO_2	202-203	$C_{25}H_{28}N_4O_4$	57.59	5.80	10.74
						·2HCl	(57.47	6.01	10.62)
30	A		N	4-NO_2	158-160	$C_{25}H_{28}N_4O_4$	52.18	6.31	9.74
						·2HCl·3H_2O	(52.31	6.19	9.59)
31	A		N	3-OCH_3	221.5-223	$C_{26}H_{31}N_3O_3$	60.58	6.65	8.15
						·2HCl·1/2H_2O	(60.44	6.59	8.03)
32	A		N	2-OCH_3	203-207	$C_{26}H_{31}N_3O_3$	59.54	6.73	8.01
						·2HCl·H_2O	(59.70	6.57	7.85)
33	A		N	4-OCH_3	219-222	$C_{26}H_{31}N_3O_3$	61.12	6.61	8.22
						·2HCl·1/4H_2O	(61.01	6.60	8.24)
34	B		CH	-	244-246	$C_{26}H_{30}N_2O_2$	69.71	6.97	6.25
						·HCl·1/2H_2O	(69.70	7.09	6.11)

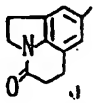
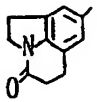
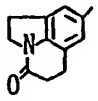
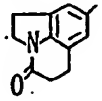
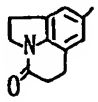
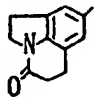
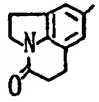
[Table 5, continued]

Comp. No.	Method	Ar	Z	X	m.p. (℃)	Molecular Formula	Elemental Analysis Calcd. (Found) C	H	N
35	A		N	3−NO_2	198−200	$C_{25}H_{28}N_4O_4$ ·2HCl·H_2O	55.66 (55.39)	5.98 6.01	10.39 10.22)
36	A		N	4−NO_2	207−211	$C_{25}H_{28}N_4O_4$ ·2HCl·1/4H_2O	57.09 (56.95	5.84 5.92	10.65 10.44).
37	B		CH	3.4−OCH_2O−	amorphous powder	$C_{27}H_{30}N_2O_4$ ·HCl·3/2H_2O	63.58 (63.56	6.72 6.60	5.49 5.23)
38	B		CH	−	amorphous powder	$C_{28}H_{30}N_2O_2$ ·HCl·1/4H_2O	70.41 (70.16	7.15 7.16	6.31 6.10)
39	B		CH	2−F	amorphous powder	$C_{26}H_{29}FN_2O_2$ ·HCl·5/2H_2O	62.21 (62.17	7.03 6.73	5.58 5.40)
40	B		CH	3−F	amorphous powder	$C_{26}H_{29}FN_2O_2$ ·HCl·5/2H_2O	62.21 (61.72	7.03 6.53	5.58 5.57)

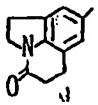
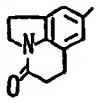
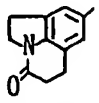
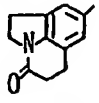
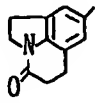
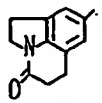
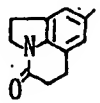
[Table 5, continued]

Comp. No.	Method	Ar	Z	X	m.p. (℃)	Molecular Formula	Elemental Analysis Calcd. (Found) C	H	N
41	B		CH	4-F	amorphous powder	$C_{26}H_{29}FN_2O_2$ ·HCl·$2H_2O$	63.34 (63.23	6.95 6.51	5.68 5.71)
42	B		CH	2-Cl	amorphous powder	$C_{26}H_{29}ClN_2O_2$ ·HCl·$5/2H_2O$	60.23 (60,62	6.80 6.45	5.40 5.38)
43	B		CH	3-Cl	amorphous powder	$C_{26}H_{29}ClN_2O_2$ ·HCl·$3/2H_2O$	62.40 (62.22	6.65 6.58	5.60 5.31)
44	B		CH	4-Cl	amorphous powder	$C_{26}H_{29}ClN_2O_2$ ·HCl·H_2O	63.54 (63.26	6.56 6.53	5.70 5.54)
45	B		CH	2-CH_3	amorphous powder	$C_{27}H_{32}N_2O_2$ ·HCl·$3/2H_2O$	67.56 (67.59	7.56 7.78	5.84 5.85)
46	B		CH	3-CH_3	amorphous powder	$C_{27}H_{32}N_2O_2$ ·HCl·$3/2H_2O$	67.56 (67.79	7.56 7.60	5.84 5.65)
47	B		CH	4-CH_3	amorphous powder	$C_{27}H_{32}N_2O_2$ ·HCl·$3/2H_2O$	67.56 (67.74	7.56 7.56	5.84 5.78)

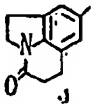
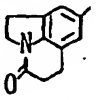
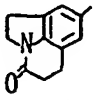
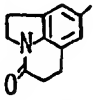
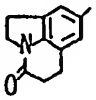
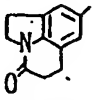
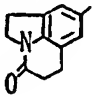
[Table 5, continued]

Comp. No.	Method	Ar	Z	X	m.p. (℃)	Molecular Formula	Elemental Analysis Calcd. (Found) C	H	N
48	B		CH	2−OCH_3	amorphous	$C_{27}H_{32}N_2O_3$	69.14	7.09	5.97
					powder	·HCl	(69.02	6.89	6.01)
49	B		CH	3−OCH_3	amorphous	$C_{27}H_{32}N_2O_3$	65.38	7.32	5.65
					powder	·HCl·3/2H_2O	(65.01	7.39	5.51)
50	B		CH	4−OCH_3	amorphous	$C_{27}H_{32}N_2O_3$	64.21	7.38	5.55
					powder	·HCl·2H_2O	(63.98	7.42	5.50)
51	B		CH	2−NO_2	amorphous	$C_{26}H_{29}N_3O_4$	59.03	6.67	7.94
					powder	·HCl·5/2H_2O	(58.88	6.75	8.01)
52	B		CH	3−NO_2	amorphous	$C_{26}H_{29}N_3O_4$	60.17	6.41	8.10
					powder	·HCl·2H_2O	(60.20	6.17	7.96)
53	B		CH	4−NO_2	amorphous	$C_{26}H_{29}N_3O_4$	64.66	6.05	8.70
					powder	·HCl	(64.52	5.97	8.64)
54	B		CH	2,4−$(CH_3)_2$	amorphous	$C_{28}H_{34}N_2O_2$	70.64	7.83	5.88
					powder	·HCl·1/2H_2O	(70.30	7.62	6.09)

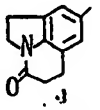
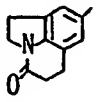
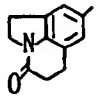
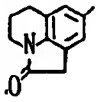
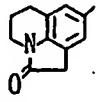
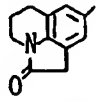
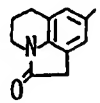
[Table 5, continued]

Comp. No.	Method	Ar	Z	X	m.p. (℃)	Molecular Formula	Elemental Analysis Calcd. (Found) C	H	N
55	B		CH	3,5-$(CH_3)_2$	amorphous	$C_{28}H_{34}N_2O_2$	69.33	7.69	5.78
					powder	$\cdot HCl \cdot H_2O$	(69.38	7.77	5.82)
56	B		CH	2,5-$(CH_3)_2$	amorphous	$C_{28}H_{34}N_2O_2$	66.85	7.81	5.57
					powder	$\cdot HCl \cdot 2H_2O$	(67.14	7.46	5.43)
57	B		CH	4-C_2H_5	amorphous	$C_{28}H_{34}N_2O_2$	69.33	7.69	5.78
					powder	$\cdot HCl \cdot H_2O$	(69.23	7.60	5.49)
58	B		CH	2-OH	amorphous	$C_{26}H_{30}N_2O_3$	66.02	7.03	5.92
					powder	$\cdot HCl \cdot H_2O$	(65.97	6.91	5.72)
59	B		CH	3-OH	amorphous	$C_{26}H_{30}N_2O_3$	64.79	7.11	5.81
					powder	$\cdot HCl \cdot 3/2H_2O$	(64.67	6.82	5.65)
60	B		CH	4-OH	amorphous	$C_{26}H_{30}N_2O_3$	63.60	7.18	5.71
					powder	$\cdot HCl \cdot 2H_2O$	(63.56	7.03	5.91)
61	B		CH	2-CN	amorphous	$C_{27}H_{28}N_3O_2$	63.71	6.73	8.25
					powder	$\cdot HCl \cdot 5/2H_2O$	(64.00	6.54	8.23)

[Table 5, continued]

Comp. No.	Method	Ar	Z	X	m.p. (℃)	Molecular Formula	Elemental Analysis Calcd. (Found) C	H	N
62	B		CH	3-CN	amorphous powder	$C_{27}H_{29}N_3O_2$ ·HCl·$2H_2O$	64.85 (64.92)	6.85 (6.88)	8.40 (8.17)
63	B		CH	4-CN	amorphous powder	$C_{27}H_{29}N_3O_2$ ·HCl·H_2O	67.28 (67.31)	6.69 (6.78)	8.72 (8.80)
64	B		CH	3,4-$(OCH_3)_2$	amorphous powder	$C_{28}H_{34}N_2O_4$ ·HCl	67.39 (67.14)	7.07 (7.10)	5.61 (5.54)
65	B		CH	2,3-$(OCH_3)_2$	amorphous powder	$C_{28}H_{34}N_2O_4$ ·HCl·3/$2H_2O$	63.93 (63.79)	7.28 (7.21)	5.33 (5.35)
66	A		N	2,3-Cl_2	229-230	$C_{25}H_{27}Cl_2N_3O_2$ ·2HCl·H_2O	53.30 (53.08)	5.55 (5.44)	7.46 (7.49)
67	A		N	2,4-Cl_2	219-221	$C_{25}H_{27}Cl_2N_3O_2$ ·2HCl·H_2O	53.30 (53.03)	5.55 (5.49)	7.46 (7.33)
68	A		N	2,6-Cl_2	209-213	$C_{25}H_{27}Cl_2N_3O_2$ ·2HCl·$2H_2O$	51.65 (51.52)	5.72 (5.63)	7.23 (7.07)

[Table 5, continued]

Comp. No.	Method	Ar	Z	X	m.p. (°C)	Molecular Formula	Elemental Analysis Calcd. (Found) C	H	N
69	A		N	3,4−Cl_2	222−224	$C_{25}H_{27}Cl_2N_3O_2$	54.17	5.45	7.58
						·2HCl·1/2H_2O	(54.46	5.52	7.55)
70	A		N	2−NO_2	216−221	$C_{25}H_{28}N_4O_4$	54.75	6.06	10.22
						·2HCl·3/2H_2O	(54.89	5.92	10.00)
71	A		N	2−OH	229−231	$C_{25}H_{29}N_3O_3$	54.95	6.82	7.69
						·2HCl·3H_2O	(55.02	6.13	7.57)
72	B		CH	3−OCH_3	amorphous	$C_{27}H_{32}N_2O_3$	67.84	7.17	5.86
					powder	·HCl·1/2H_2O	(67.56	7.05	5.80)
73	B		CH	4−OCH_3	amorphous	$C_{27}H_{32}N_2O_3$	67.21	7.21	5.81
					powder	·HCl·3/4H_2O	(67.11	6.95	5.95)
74	B		CH	3,4−$(OCH_3)_2$	amorphous	$C_{28}H_{34}N_2O_4$	62.85	7.35	5.24
					powder	·HCl·2H_2O	(62.77	7.61	5.31)
75	B		CH	4−C_2H_5	amorphous	$C_{28}H_{34}N_2O_2$	69.33	7.69	5.78
					powder	·HCl·H_2O	(69.50	7.48	5.80)

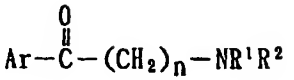
[Table 5, continued]

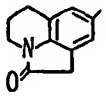
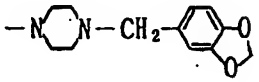
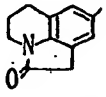
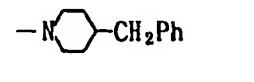
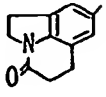
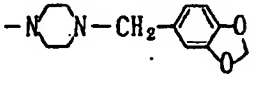
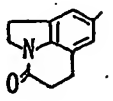
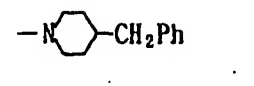
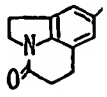
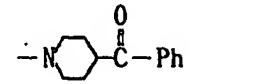
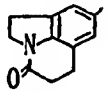
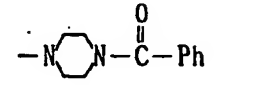
Comp. No.	Method	Ar	Z	X	m.p. (°C)	Molecular Formula	Elemental Analysis Calcd. (Found) C	H	N
76	B		CH	3.5-$(CH_3)_2$	amorphous powder	$C_{28}H_{34}N_2O_2$ ·HCl·$2H_2O$	66.85 (66.79)	7.81 (7.58)	5.57 (5.53)

Example 25

[0138] Using the compound as obtained in Reference Example 4 or 6, the same procedure as in Example 1 was followed to yield the compounds listed in Table 6 compounds 1-10.

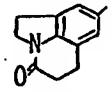
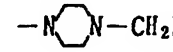
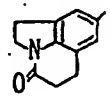
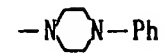
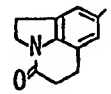
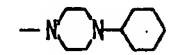
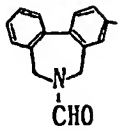
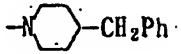
[Table 6]



Comp. No.	Ar	n	NR^1R^2	m.p. (℃)	Molecular Formula	Elemental Analysis Calcd. (Found) C	H	N
1		2		215−217	$C_{26}H_{29}N_3O_4$	58.98	6.09	7.94
					$\cdot 2HCl \cdot 1/2H_2O$	(59.18	6.03	7.95)
2		2		218−220	$C_{26}H_{30}N_2O_2$	69.71	7.20	6.23
					$\cdot HCl \cdot 1/2H_2O$	(69.97	7.10	6.30)
3		2		230−235	$C_{26}H_{29}N_3O_4$	58.48	6.13	7.87
					$\cdot 2HCl \cdot 3/4H_2O$	(58.36	6.08	7.80)
4		2		241−243	$C_{26}H_{30}N_2O_2$	70.41	7.16	6.32
					$\cdot HCl \cdot 1/4H_2O$	(70.58	7.18	6.39)
5		2		236−237	$C_{26}H_{28}N_2O_3$	68.26	6.50	6.12
					$\cdot HCl \cdot 1/4H_2O$	(68.28	6.52	5.99)
6		2		204−208	$C_{25}H_{27}N_3O_3$	64.86	6.31	9.08
					$\cdot HCl \cdot 1/2H_2O$	(64.65	6.50	8.80)

[Table 6, continued]

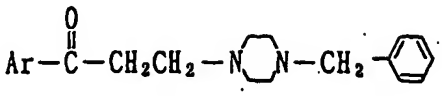
$Ar-\overset{\overset{O}{\|}}{C}-(CH_2)_n-NR^1R^2$

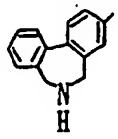
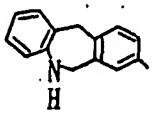
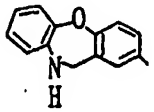
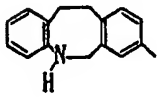
Comp. No.	Ar	n	NR^1R^2	m.p. (℃)	Molecular Formula	Elemental Analysis Calcd. (Found) C	H	N
7		3		201−205	$C_{26}H_{31}N_3O_2$ ·2HCl·3/2H_2O	60.35 (60.66	7.01 7.03	8.12 8.12)
8		3		234−236	$C_{25}H_{29}N_3O_2$ ·2HCl·1/2H_2O	61.85 (62.14	6.64 6.57	8.66 8.65)
9		3		226−229	$C_{25}H_{35}N_3O_2$ ·2HCl·3H_2O	55.97 (56.02	8.08 8.10	7.83 7.84)
10		2		amorphous powder	$C_{30}H_{32}N_2O_2$ ·HCl·3/2H_2O	69.82 (69.78	7.03 6.92	5.43 5.16)

Example 26

[0139] Using the compound as obtained in Example 12, the same procedure as in Example 2 was followed to yield the compounds listed in Table 7,

[Table 7]

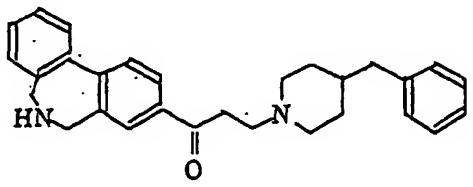


Comp. No.	Ar	m.p. (°C)	Molecular Formula	Elemental Analysis Calcd. (Found) C	H	N
1		184−187	$C_{28}H_{31}N_3O$ ·3HCl·5/2H_2O	57.98 (58.28	6.78 6.64	7.24 7.39)
2		178−181	$C_{28}H_{31}N_3O$ ·3HCl	62.86 (62.61	6.41 6.45	7.86 7.78)
3		178−183	$C_{27}H_{29}N_3O_2$ ·3HCl·2H_2O	56.60 (56.73	6.33 6.39	7.33 7.23)
4		amorphous powder	$C_{29}H_{33}N_3O$ ·3HCl·H_2O	61.43 (61.54	6.76 6.61	7.41 7.14)

Example 27

1-(6,7-Dihydro-5H-dibenz[c,e]azepin-3-yl)-3-[4-(phenylmethyl)-1-piperidinyl]-1-propanone dihydrochloride

[0140]



·2HCl

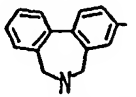
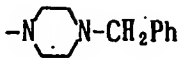
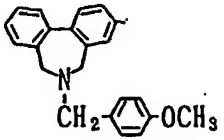
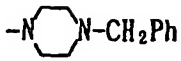
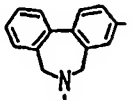
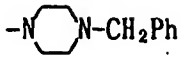
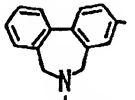
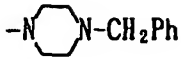
[0141] Using the compound No. 10 in Example 25, the same procedure as in Example 2 was followed to yield the title compound as an amorphous poweder.

Elemental analysis (for $C_{29}H_{32}N_2O \cdot 2HCl \cdot 2H_2O$):			
Calculated	C, 65.28;	H, 7.18;	N, 5.25
Found	C, 65.22;	H, 7.08;	N, 5.08

Example 28

[0142] Using the compound as obtained in Example 26 or 27, the same procedure as in Example 4 (method A) or Example 6 (method B) was followed to yield the compounds listed in Table 8.

[Table 8 i]

Comp. No.	Method	Ar	NR^1R^2	m.p. (℃)	Molecular Formula	Elemental Analysis Calcd. (Found) C	H	N
1	A			203—206 (decomp.)	$C_{36}H_{37}N_3O$ ·3HCl·5/2H_2O	62.73 (62.49)	6.77 (6.62)	6.27 (6.23)
2	A			193—196 (decomp.)	$C_{36}H_{39}N_3O_2$ ·3HCl	66.00 (65.82)	6.46 (6.59)	6.41 (6.43)
3	B			149—152	$C_{30}H_{33}N_3O_2$ ·2HCl·3H_2O	60.60 (60.64)	6.95 (6.98)	7.07 (7.22)
4	B			151—161	$C_{35}H_{35}N_3O_2$ ·2HCl·2H_2O	65.82 (66.11)	6.47 (6.46)	6.58 (6.28)

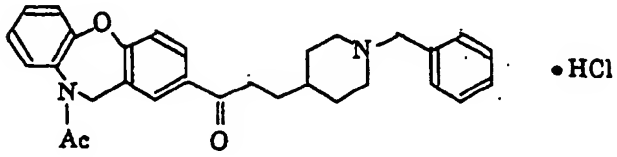
[Table 8, continued]

Comp. No.	Method	Ar	NR^1R^2	m.p. (°C)	Molecular Formula	Elemental Analysis Calcd. (Found) C	H	N
5	B			191–194 (decomp.)	$C_{36}H_{37}N_3O_3$ ·2HCl	68.35 (68.08)	6.21 6.32	6.64 6.63
6	B			amorphous powder	$C_{31}H_{34}N_2O_2$ ·HCl	74.01 (73.83)	7.01 6.98	5.57 5.45
7	A			amorphous powder	$C_{36}H_{38}N_2O$ ·2HCl	71.39 (71.12)	6.99 7.05	4.63 4.54
8	B			amorphous powder	$C_{36}H_{36}N_2O_2$ ·HCl·3/2H_2O	73.02 (72.77)	6.81 6.53	4.73 4.51

Example 29

. 1-(10-Acetyl-10,11-dihydrodibenz[b,f][1,4]oxazepin -2-yl)-3[1-(phenylmethyl)-4-piperidinyl]-1-propanone hydrochloride

[0143]



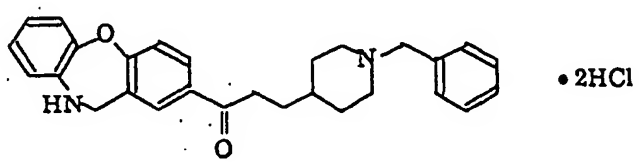
[0144] Using the known compound, 10-acetyl-10,11-dihydrodibenz[b,f][1,4]oxazepine, the same procedures as in Example 3 and then Example 4 were followed to yield the title compound as a colorless amorphous powder.

Elemental analysis (for $C_{30}H_{32}N_2O_3 \cdot HCl$):			
Calculated	C, 71.35;	H, 6.59;	N, 5.55
Found	C, 71.21;	H, 6.63;	N, 5.50

Example 30

1-(10,11-Dihydrodibenz[b,f][1,4]oxazepin-2-yl)-3-[1-(phenylmethyl)-4-piperidinyl]-1-propanone dihydrochloride

[0145]



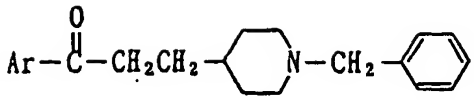
[0146] Using 1-(10-acetyl-10,11-dihydrodibenz[b,f][1,4]oxazepin-2-yl)-3-[1-(phenylmethyl)-4-piperidinyl]-1-propanone hydrochloride obtained in Example 35, the same procedure as in Example 12 was followed to yield the title compound as colorless crystals having a melting point of 144-147°C (decomposition).

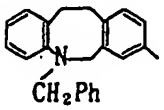
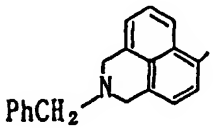
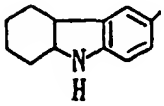
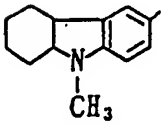
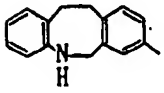
Elemental analysis (for $C_{28}H_{30}N_2O_2 \cdot 2HCl \cdot 3/2H_2O$):			
Calculated	C, 63.88;	H, 6.70;	N, 5.32
Found	C, 63.98;	H, 6.48;	N, 5.44

Example 31

[0147] Using the known compounds, the same procedures as in Example 3 and then Example 4 were followed to yield the compounds listed in Table 9.

[Table 9]



Comp. No.	Ar	m.p. (℃)	Molecular Formula	Elemental Analysis Calcd. (Found) C	H	N
1		171-173	$C_{37}H_{40}N_2O$ ·$C_4H_4O_4$·1/2H_2O	75.32 (75.21	6.94 7.06	4.28 4.06)
2		amorphous powder	$C_{34}H_{36}N_2O$ ·$2C_4H_4O_4$·H_2O	68.28 (68.15	6.28 6.39	3.79 3.71)
3		amorphous powder	$C_{27}H_{34}N_2O$ ·$2C_4H_4O_4$	66.23 (66.18	6.67 6.70	4.41 4.40)
4		amorphous powder	$C_{28}H_{36}N_2O$ ·$2C_4H_4O_4$	66.65 (66.41	6.84 6.59	4.32 4.24)
5		amorphous powder	$C_{30}H_{34}N_2O$ ·2HCl·H_2O	68.04 (68.42	7.23 7.62	5.29 4.99)

Formulation Example 1

[0148]

(1) 1-(1,2,2a,3,4,5-hexahydrobenz[cd]indol-6-yl)-3-[1-(phenylmethyl)piperidin-4-yl]-1-propanone dihydrochloride (compound of Example 4)	1 g
(2) Lactose	197 g

(continued)

(3) Corn starch	50 g
(4) Magnesium stearate	2 g

[0149] 1 g of compound (1), 197 g of lactose (2) and 20 g of corn starch (3) were uniformly mixed and granulated with a paste prepared from 15 g of corn starch and 25 ml of water. After 15 g of corn starch and 2 g of magnesium stearate (4) were added, the granules were tableted, using a compressive tableting machine, to yield 2000 tablets containing 0.5 mg of compound (1) per tablet and having a diameter of 3 mm.

Formulation Example 2

[0150]

(1) 1-(1,2,2a,3,4,5-hexahydrobenz[cd]indol-6-yl)-3-[1-(phenylmethyl)piperidin-4-yl]-1-propanone dihydrochloride (compound of Example 4)	2 g
(2) Lactose	197 g
(3) Corn starch	50 g
(4) Magnesium stearate	2 g

[0151] 2 g of compound (1), 197 g of lactose (2) and 20 g of corn starch (3) were uniformly mixed and granulated with a paste prepared from 15 g of corn starch and 25 ml of water. After 15 g of corn starch and 2 g of magnesium stearate (4) were added, the granules were tableted, using a compressive tableting machine, to yield 2000 tablets containing 1.0 mg of compound (1) per tablet and having a diameter of 3 mm.

Experimental Example 1

[0152] The cholinesterase inhibitory activity of the compound of the present invention was tested, using (acetyl-[^{3}H])-acetylcholine. Using the S_1 fraction of a male Wistar rat cerebral cortex homogenate as a source of cholinesterase, (acetyl-[^{3}H])-acetylcholine, as a substrate, and the test compound, as a sample, were incubated for 30 minutes. After the reaction was terminated, a toluene scintillator was added and the reaction mixture was shaken to migrate the [^{3}H]-acetic acid resulting from the reaction to the toluene layer, where radioactivity was counted using a liquid scintillation counter to determine the cholinesterase inhibitory activity.

[0153] The sample's cholinesterase inhibitory activity was expressed by 50% inhibitory concentration (IC_{50}). The cholinesterase inhibitory activity of physostigmine was determined by the same method.

[0154] The results are given in Table 10

Table 10

Compound (Example No.)	Acetylcholinesterase Inhibitory Activity IC_{50} (μM)
4	0.0918
11-1	0.154
12-1	0.0030
12-2	0.0076
12-3	0.0172
12-4	0.0095
12-5	0.0454
12-6	0.0151
12-7	0.0330
12-8	0.0470
12-9	0.0968
14-1	0.182
17	0.0614
24-1	0.0287
24-3	0.0109

Table 10 (continued)

Compound (Example No.)	Acetylcholinesterase Inhibitory Activity IC_{50} (μM)
24-4	0.0430
24-10	0.0189
24-11	0.0169
24-12	0.0239
24-13	0.1297
24-16	0.0058
24-18	0.0249
24-19	0.0119
24-21	0.0036
24-22	0.0062
24-24	0.0015
24-25	0.000098
24-26	0.0044
24-27	0.188
24-29	0.0293
24-32	0.0911
24-34	0.0005
24-35	0.0679
24-38	0.00018
24-39	0.00050
24-40	0.000092
24-41	0.00047
24-42	0.00054
24-43	0.000065
24-44	0.0599
24-45	0.000304
24-46	0.000200
24-47	0.0195
24-48	0.0171
24-52	0.00036
24-53	0.0254
24-54	0.0609
24-56	0.0183
24-58	0.00012
24-59	0.00112
24-60	0.000078
24-61	0.0156
25-4	0.188
25-1	0.0024
25-2	0.115
25-3	0.0590
28-1	0.0393
28-2	0.0200
28-3	0.171
28-5	0.0316
31-2	0.184
31-4	0.136
31-5	0.081
Physostigmine	0.220

[0155] From Table 10, it is seen that the compound of the present invention is more potent than physostigmine in acetylcholinesterase inhibition.

Experimental Example 2

[0156] Effects of the compound of this invention on monoamine uptake were investigated using [^{3}H] - norepinephirine (NE) and [^{3}H] - serotonin (5-HT). Rats were sacrificed by decapitation. The cerebral cortex and hippocampus were removed and homogenized in 10-15 volumes (W/V) of an ice-cold medium containing 0.32 M sucrose. Crude synaptosomal preparations (P2) were isolated after differential centrifugation at 1000 x g for 10 min and 20,000 x g for 30 min at 4°C. Synaptosomal membranes were suspended in Krebs-Ringer bicarbonate (KRB) solution (116 mM NaCl, 4.8 mM KCl, 1.3 mM $CaCl_2$, 1.2 mM $MgSO_4$, 1.2 mM NaH_2PO_4, 25 mM $NaHCO_3$, 0.1 mM EDTA-2Na, 11.1 mM D-glucose, 0.11 mM L-ascorbic acid, 0.01 mM pargyline). Synaptosomal membrane suspension (900 µl) was preincubated with the test compound dissolved in DMSO solution at 37°C. for 5 min. The reaction was initiated by addition of 100 µl of [^{3}H] - NE (11 nM in final concentration) or [^{3}H] - HT (10 nM in final concentration). Five minutes later, the reaction was stopped by the addition of 4 ml of ice-cold KRB and the reaction mixture was filtered through Whatman CF/B. Filters were washed twice with 4 ml of KRB and the radioactivity bound was counted with liquid scintillant. Imipramine was used as positive control. All compounds were tested at 10^{-8}, 10^{-7}, 10^{-6} and 10^{-5}M. The results are shown in Table 11.

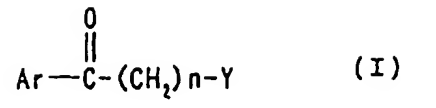
Table 11

Compound (Example No.)	Monoamine Reuptake Inhibitory Activity IC_{50} (µM)	
	NE	5-HT
2	0.420	0.594
4	0.347	0.601
13-1	0.328	1.67
17	2.43	0.0668
24-1	4.6	0.0956
24-6	5.96	0.0863
24-8	0.643	0.0607
24-19	2.82	0.066
24-21	1.54	0.0882
24-22	0.795	0.0601
24-25	1.31	0.0117
24-27	0.559	0.0798
24-28	2.81	0.0615
24-36	7.48	0.0468
25-1	6.183	0.0463
25-2	0.0738	0.00879
25-4	0.16	0.0207
25-11	0.515	0.0695
28-4	0.456	0.969
28-6	0.481	0.0806
28-8	0.197	0.363
Imipramine	1.12	0.063

[0157] From Table 11, it is seen that the compounds of the present invention are as potent as imipramine in monoamine reuptake inhibition.

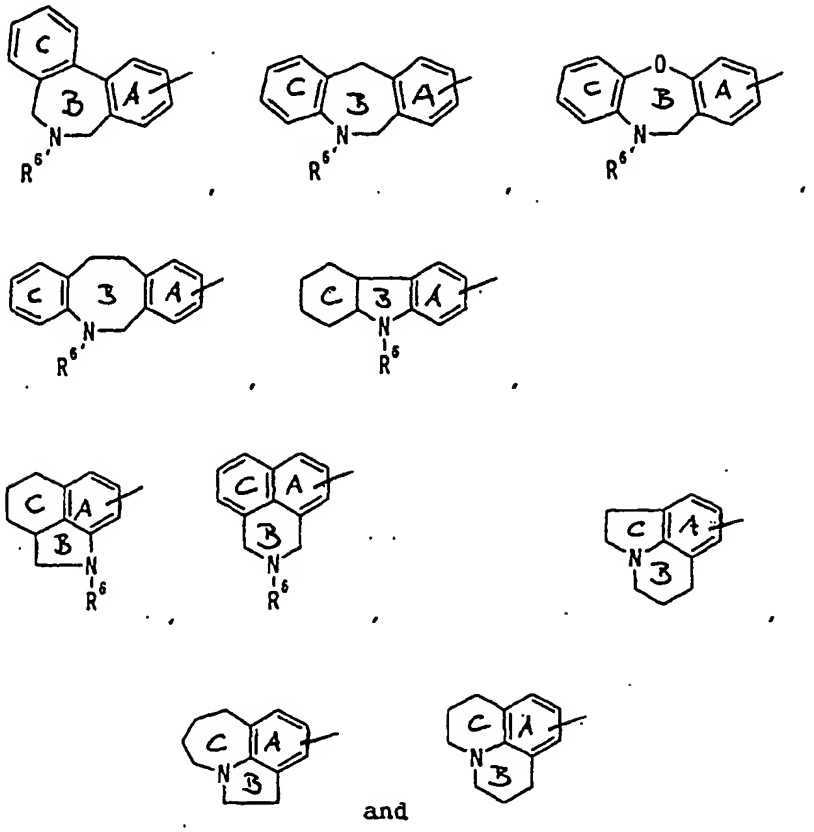
Claims

1. A compound of the formula:



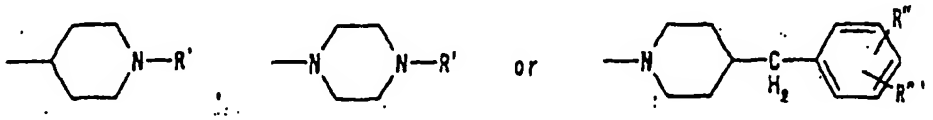
(I)

wherein Ar is selected from the group consisting of the formula:



and

wherein ring A has no substituent, and
wherein ring B or C is optionally subsituted by an oxo and/or C_{1-6} alkyl, and
R^6 is hydrogen, C_{1-6} alkyl, formyl, C_{1-6} alkyl-carbonyl, benzoyl or benzyl optionally substituted by C_{1-4} alkoxy;
Y is a group of the formula:



wherein

R' is (1) a benzyl which may be substituted with 1 or 2 substituents selected from the group consisting of C_{1-6} alkyl, halogen, nitro, cyano, amino, mono- or di-C_{1-6} alkylamino, hydroxy, C_{1-6} alkoxy, phenyl-C_{1-4} alkoxy and C_{1-4} alkylenedioxy, (2)cyclohexyl, (3) phenyl, (4) formyl, (5) C_{1-6} alkyl-carbonyl, (6) benzoyl or (7) C_{1-6} alkoxy-carbonyl or (8) hydrogen;

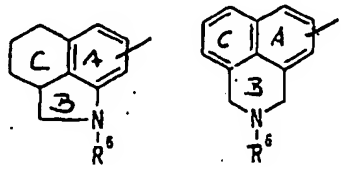
R" and R"' are the same or different and are hydrogen, C_{1-6} alkyl, halogen, nitro, cyano, hydroxy, C_{1-6} alkoxy,

phenyl-C_{1-4} alkoxy or C_{1-4} alkylenedioxy;
n is an integer of 2 or 3 ,

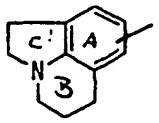
or a salt thereof.

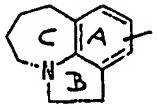
2. A compound as claimed in claim 1, wherein Y is a 4-piperidinyl or 1-piperazinyl group which is optionally substituted by (i) cyclohexyl, (ii) phenyl, (iii) benzyl optionally substituted by 1 or 2 subtituents selected from the group consisting of halogen, C_{1-6} alkyl, C_{1-6} alkoxy, hydroxy, nitro, amino and cyano, (iv) C_{1-6} alkoxy-carbonyl, (v) C_{1-6} alkyl-carbonyl, (vi) benzoyl or (vii) formyl.

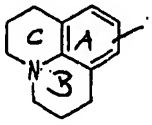
3. A compound as claimed in claim 1, wherein Ar is selected from the group consisting of the formula:



,

,


,




and

wherein ring A, ring B, ring C and R^6 have the same definitions as in claim 1.

4. A compound as claimed in claim 1, wherein Ar is

1,2,2a,3,4,5-hexahydrobenz[cd]indol-6-yl,
1-formyl-1,2,2a,3,4,5-hexahydrobenz[cd]indol-6-yl,
5,6-dihydro-2(1H)-oxo-4H-pyrrolo[3,2,1-ij]quinolin-8-yl,
4-oxo-1,2,5,6-tetrahydro-4H-pyrrolo[3,2,1-ij]quinolin-8-yl,
1,2,4,5,6,7-hexahydro-2-oxoazepino[3,2,1-hi]indol-9-yl or
2,3,6,7-tetrahydro-5-oxo-1H,5H-benzo[ij]quinolizin-9-yl.

5. A compound as claimed in claim 1, wherein Y is a 1-benzyl-4-piperidinyl, 4-benzyl-1-piperazinyl or 4-benzyl-1-piperidinyl.

6. A compound as claimed in claim 1, which is

8-[3-[4-[(3-methylphenyl)methyl]-1-piperazinyl]-1-oxopropyl]-1,2,5,6-tetrahydro-4H-pyrrolo[3,2,1-ij]quinolin-4-one or a salt thereof,
8-[3-[4-[(3-chlorophenyl)methyl]-1-piperazinyl]-1-oxopropyl]-1,2,5,6-tetrahydro-4H-pyrrolo[3,2,1-ij]quinolin-4-one or a salt thereof,
8-[3-[4-[(2-methylphenyl)methyl]-1-piperazinyl]-1-oxopropyl]-5,6-dihydro-4H-pyrrolo[3,2,1-ij]quinolin-2(1H)-one or a salt thereof,
8-[3-[4-[(3-chlorophenyl)methyl]-1-piperazinyl]-1-oxopropyl]-5,6-dihydro-4H-pyrrolo[3,2,1-ij]quinolin-2(1H)-one or a salt thereof,
8-[3-[1-(phenylmethyl)-4-piperidinyl]-1-oxopropyl]-1,2,5,6-tetrahydro-4H-pyrrolo[3,2,1-ij]quinolin-4-one or a salt thereof,
8-[3-[1-[(4-methylphenyl)methyl]-4-piperidinyl]-1-oxopropyl]-1,2,5,6-tetrahydro-4H-pyrrolo[3,2,1-ij]quinolin-4-one or a salt thereof,
8-[3-[1-[(3-methoxyphenyl)methyl]-4-piperidinyl]-1-oxopropyl]-1,2,5,6-tetrahydro-4H-pyrrolo[3,2,1-ij]quinolin-4-one or a salt thereof,

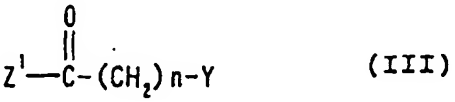
8-[3-[1-[(2,4-dimethylphenyl)methyl]-4-piperidinyl]-1-oxopropyl]-1,2,5,6-tetrahydro-4H-pyrrolo[3,2,1-ij]quinolin-4-one or a salt thereof,
8-[3-[1-[(2,5-dimethylphenyl)methyl]-4-piperidinyl]-1-oxopropyl]-1,2,5,6-tetrahydro-4H-pyrrolo[3,2,1-ij]quinolin-4-one or a salt thereof,
8-[3-[1-[(4-chlorophenyl)methyl]-4-piperidinyl]-1-oxopropyl]-1,2,5,6-tetrahydro-4H-pyrrolo[3,2,1-ij]quinolin-4-one or a salt thereof,
8-[3-[1-[(4-nitrophenyl)methyl]-4-piperidinyl]-1-oxopropyl]-1,2,5,6-tetrahydro-4H-pyrrolo[3,2,1-ij]quinolin-4-one or a salt thereof,
8-[3-[1-[(phenylmethyl)methyl]-4-piperidinyl]-1-oxopropyl]-5,6-dihydro-4H-pyrrolo[3,2,1-ij]quinolin-2(1H)-one or a salt thereof,
8-[3-[1-[(3-methoxyphenyl)methyl]-4-piperidinyl]-1-oxopropyl]-5,6-dihydro-4H-pyrrolo[3,2,1-ij]quinolin-2(1H)-one or a salt thereof,
8-[3-[4-(phenylmethyl)-1-piperidinyl]-1-oxopropyl]-1,2,5,6-tetrahydro-4H-pyrrolo[3,2,1-ij]quinolin-4-one or a salt thereof.
8-[3-[4-(phenylmethyl)-1-piperidinyl]-1-oxopropyl]-5,6-dihydro-4H-pyrrolo[3,2,1-ij]quinolin-2(1H)-one or a salt thereof.
1-(1,2,2a,3,4,5-hexahydrobenz[cd]indol-6-yl)-3-[1-(phenylmethyl)piperidin-4-yl]-1-propanone or a salt thereof,
1-(1-methyl-1,2,2a,3,4,5-hexahydrobenz[cd]indol-6-yl)-3-[1-(phenylmethyl)piperidin-4-yl]-1-propanone or a salt thereof,
1-[2-(phenylmethyl)-2,3-dihydro-1H-benz[de]isoquinolin-6-yl]-3-[1-(phenylmethyl)-4-piperidinyl]-1-propanone or a salt thereof,
8-[3-[1-[(3-fluorophenyl)methyl]-4-piperidinyl]-1-oxopropyl]-1,2,5,6-tetrahydro-4H-pyrrolo[3,2,1-ij]quinolin-4-one or a salt thereof, or
8-[3-[1-[(2-hydroxyphenyl)methyl]-4-piperidinyl]-1-oxopropyl]-1,2,5,6-tetrahydro-4H-pyrrolo[3,2,1-ij]quinolin-4-one or a salt thereof.

7. A method for producing the compound of claim 1, which comprises

1) reacting a compound of the formula:

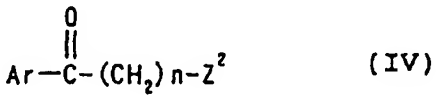
$$Ar\text{-}H \qquad (II)$$

wherein Ar has the same definition as in claim 1, or a salt thereof, with a compound of the formula:



$$Z^1\text{—}C\text{-}(CH_2)n\text{-}Y \qquad (III)$$

wherein Z^1 is a leaving group and the other symbols have the same definitions as in claim 1, or a salt thereof, or
2) reacting a compound of the formula:



$$Ar\text{—}C\text{-}(CH_2)n\text{-}Z^2 \qquad (IV)$$

or a salt thereof, with a compound of the formula:

$$Z^3\text{-}Y \qquad (V)$$

wherein Z^2 and Z^3 are groups capable of reacting with each other to be removed; and the other symbols have

the same definitions as in claim 1, or a salt thereof.

8. A pharmaceutical composition which contains a compound as claimed in claim 1.

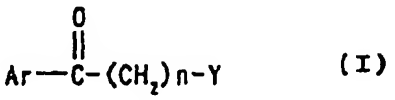
9. Use of a compound as claimed in claim 1 or a pharmaceutically acceptable salt thereof, as a component in the preparation of a cholinesterase inhibitory composition.

10. A cholinesterase inhibitory composition which contains an effective cholinesterase inhibiting amount of a compound as claimed in claim 1 or a pharmaceutically acceptable salt thereof and a pharmacologically acceptable carrier.

11. A composition as claimed in claim 10, for use in the treatment of senile dementia and/or Alzheimer's disease.

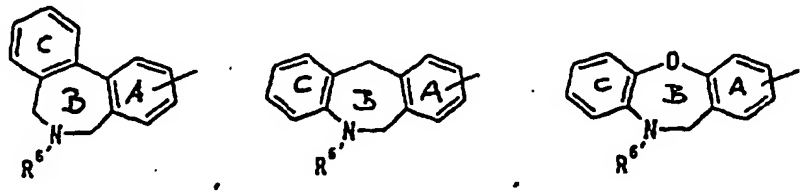
Patentansprüche

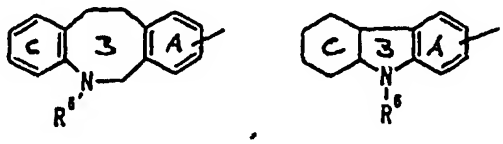
1. Verbindung der Formel

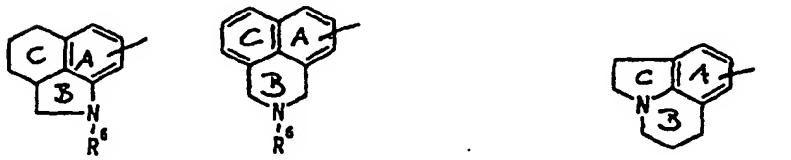


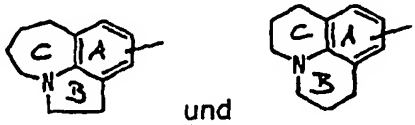
(I)

worin Ar aus der Gruppe ausgewählt ist, die aus den Formeln





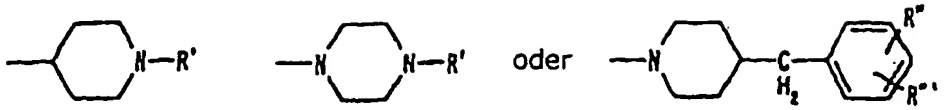




und

besteht, worin Ring A keinen Substituenten aufweist und
worin Ring B oder C gegebenenfalls durch ein Oxo und/oder C_{1-6}-Alkyl substituiert ist und
R^6 Wasserstoff, C_{1-6}-Alkyl, Formyl, C_{1-6}-Alkylcarbonyl, Benzoyl oder gegebenenfalls durch C_{1-4}-Alkoxy substitu-

iertes Benzyl ist;
Y eine Gruppe der Formel



ist, worin

R' (1) Benzyl, das mit 1 oder 2 Substituenten substituiert sein kann, die aus der aus C_{1-6}-Alkyl, Halogen, Nitro, Cyan, Amino, Mono- oder Di-C_{1-6}alkylamino, Hydroxy, C_{1-6}-Alkoxy, Phenyl-C_{1-6}-alkoxy und C_{1-4}-Alkylendioxy bestehenden Gruppe ausgewählt sind, (2) Cyclohexyl, (3) Phenyl, (4) Formyl, (5) C_{1-6}-Alkylcarbonyl, (6) Benzolyl oder (7) C_{1-6}-Alkoxycarbonyl oder (8) Wasserstoff ist;

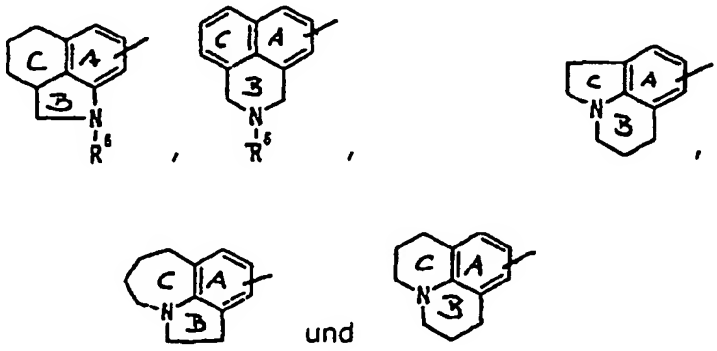
R" und R"' gleich oder verschieden sind und Wasserstoff, C_{1-6}-Alkyl, Halogen, Nitro, Cyan, Hydroxy, C_{1-6}-Alkoxy, Phenyl-C_{1-4}-alkoxy oder C_{1-4}-Alkylendioxy sind;

n eine ganze Zahl 2 oder 3 ist,

oder ein Salz davon.

2. Verbindung wie in Anspruch 1 beansprucht, wobei Y eine 4-Piperidinyl- oder 1-Piperazinylgruppe ist, die gegebenenfalls durch (i) Cyclohexyl, (ii) Phenyl, (iii) Benzyl, das gegebenenfalls durch 1 oder 2 Substituenten substituiert ist, die aus der aus Halogen, C_{1-6}-Alkyl, C_{1-6}-Alkoxy, Hydroxy, Nitro, Amino und Cyan bestehenden Gruppe ausgewählt sind, (iv) C_{1-6}-Alkoxycarbonyl, (v) C_{1-6}-Alkylcarbonyl, (vi) Benzoyl oder (vii) Formyl substituiert ist.

3. Verbindung wie in Anspruch 1 beansprucht, wobei Ar aus der aus den Formeln



bestehenden Gruppe ausgewählt ist, worin Ring A, Ring B, Ring C und R^6 dieselben Definitionen wie in Anspruch 1 aufweisen.

4. Verbindung wie in Anspruch 1 beansprucht, wobei Ar 1,2,2a,3,4,5-Hexahydrobenz[cd]indol-6-yl, 1-Formyl-1,2,2a,3,4,5-hexahydrobenz[cd]indol-6-yl, 5,6-Dihydro-2(1H)-oxo-4H-pyrrolo[3,2,1-ij]chinolin-8-yl, 4-Oxo-1,2,5,6-tetrahydro-4H-pyrrolo[3,2,1-ij]chinolin-8-yl, 1,2,4,5,6,7-Hexahydro-2-oxoazepino[3,2,1-hi]indol-9-yl oder 2,3,6,7-Tetrahydro-5-oxo-1H,5Hbenzo[ij]chinolizin-9-yl ist.

5. Verbindung wie in Anspruch 1 beansprucht, wobei Y 1-Benzyl-4-piperidinyl, 4-Benzyl-1-piperazinyl oder 4-Benzyl-1-piperidinyl ist.

6. Verbindung wie in Anspruch 1 beansprucht, die

8-[3-[4-[(3-Methylphenyl)methyl]-1-piperazinyl]-1-oxopropyl]-1,2,5,6-tetrahydro-4H-pyrrolo[3,2,1-ij]chinolin-4-on oder ein Salz davon,

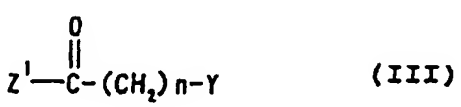
8-[3-[4-[(3-Chlorphenyl)methyl]-1-piperazinyl]-1-oxopropyl]-1,2,5,6-tetrahydro-4H-pyrrolo[3,2,1-ij]chinolin-4-on oder ein Salz davon,
8-[3-[4-[(2-Methylphenyl)methyl]-1-piperazinyl]-1-oxopropyl]-5,6-dihydro-4Hpyrrolo[3,2,1-ij]chinolin-2(1H)-on oder ein Salz davon,
8-[3-(4-[(3-Chlorphenyl)methyl]-1-piperazinyl]-1-oxopropyl]-5,6-dihydro-4Hpyrrolo[3,2,1-ij]chinolin-2(1H)-on oder ein Salz davon,
8-[3-[1-(Phenylmethyl)-4-piperidinyl]-1-oxopropyl]-1,2,5,6-tetrahydro-4Hpyrrolo[3,2,1-ij]chinolin-4-on oder ein Salz davon,
8-[3-[1-[(4-Methylphenyl)methyl]-4-piperidinyl)-1-oxopropyl)-1,2,5,6-tetrahydro-4H-pyrrolo[3,2,1-ij]chinolin-4-on oder ein Salz davon,
8-[3-(1-[(3-Methoxyphenyl)methyl]-4-piperidinyl]-1-oxopropyl]-1,2,5,6-tetrahydro-4H-pyrrolo[3,2,1-ij]chinolin-4-on oder ein Salz davon,
8-[3-[1-[(2,4-Dimethylphenyl)methyl]-4-piperidinyl]-1-oxopropyl]-1,2,5,6-tetrahydro-4H-pyrrolo[3,2,1-ij]chinolin-4-on oder ein Salz davon,
8-[3-[1-[(2,5-Dimethylphenyl)methyl]-4-piperidinyl]-1-oxopropyl]-1,2,5,6-tetrahydro-4H-pyrrolo[3,2,1-ij]chinolin-4-on oder ein Salz davon,
8-[3-[1-((4-Chlorphenyl)methyl]-4-piperidinyl]-1-oxopropyl]-1,2,5,6-tetrahydro-4H-pyrrolo[3,2,1-ij]chinolin-4-on oder ein Salz davon,
8-[3-[1-[(4-Nitrophenyl)methyl]-4-piperidinyl]-1-oxopropyl]-1,2,5,6-tetrahydro-4H-pyrrolo[3,2,1-ij]chinolin-4-on oder ein Salz davon,
8-[3-[1-[(Phenylmethyl)methyl]-4-piperidinyl]-1-oxopropyl]-5,6-dihydro-4Hpyrrolo[3,2,1-ij]chinolin-2(1H)-on oder ein Salz davon,
8-[3-[1-[(3-Methoxyphenyl)methyl]-4-piperidinyl]-1-oxopropyl]-5,6-dihydro-4Hpyrrolo[3,2,1-ij]chinolin-2(1H)-on oder ein Salz davon,
8-[3-(4-(Phenylmethyl)-1-piperidinyl]-1-oxopropyl]-1,2,5,6-tetrahydro-4Hpyrrolo[3,2,1-ij]chinolin-4-on oder ein Salz davon,
8-[3-[4-(Phenylmethyl)-1-piperidinyl]-1-oxopropyl]-5,6-dihydro-4Hpyrrolo[3,2,1-ij]chinolin-2(1H)-on oder ein Salz davon,
1-(1,2,2a,3,4,5-Hexahydrobenz[cd]indol-6-yl)-3-[1-(phenylmethyl)piperidin-4-yl]-1-propanon oder ein Salz davon,
1-(1-Methyl-1,2,2a,3,4,5-hexahydrobenz[cd]indol-6-yl)-3-[1-(phenylmethyl)-piperidin-4-yl]-1-propanon oder ein Salz davon,
1-[2-(Phenylmethyl)-2,3-dihydro-lH-benz[de]isochinolin-6-yl]-3-[1-(phenylmethyl)-4-piperidinyl)-1-propanon oder ein Salz davon,
8-[3-[1-[(3-Fluorphenyl)methyl]-4-piperidinyl]-1-oxopropyl]-1,2,5,6-tetrahydro-4H-pyrrolo[3,2,1-ij]chinolin-4-on oder ein Salz davon,
8-[3-[1-[(2-Hydroxyphenyl)methyl]-4-piperidinyl]-1-oxopropyl]-1,2,5,6-tetrahydro-4H-pyrrolo[3,2,1-ij]chinolin-4-on oder ein Salz davon ist.

7. Verfahren zum Herstellen der Verbindung des Anspruchs 1, das

1) das Umsetzen einer Verbindung der Formel

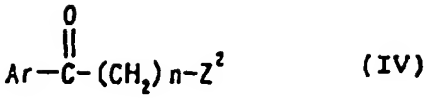
Ar-H (II)

worin Ar dieselbe Definition wie in Anspruch 1 aufweist, oder eines Salzes davon mit einer Verbindung der Formel



(III)

worin Z^1 eine Abgangsgruppe ist und die anderen Symbole dieselben Definitionen wie in Anspruch 1 aufweisen, oder einem Salz davon oder
2) das Umsetzen einer Verbindung der Formel



(IV)

oder eines Salzes davon mit einer Verbindung der Formel

(V)

worin Z^2 und Z^3 Gruppen sind, die miteinander reagieren können, um entfernt zu werden, und die anderen Symbole dieselben Definitionen wie in Anspruch 1 aufweisen, oder einem Salz davon umfaßt.

8. Pharmazeutische Zusammensetzung, die eine in Anspruch 1 beanspruchte Verbindung enthält.

9. Verwendung einer in Anspruch 1 beanspruchten Verbindung oder eines pharmazeutischen annehmbaren Salzes davon als Bestandteil bei der Herstellung einer Cholinesteraseinhibitorzusammensetzung.

10. Cholinesteraseinhibitorzusammensetzung, die eine wirksame, Cholinesterase hemmende Menge einer in Anspruch 1 beanspruchten Verbindung oder eines pharmazeutischen annehmbaren Salzes davon und einen pharmakologisch annehmbaren Träger enthält.

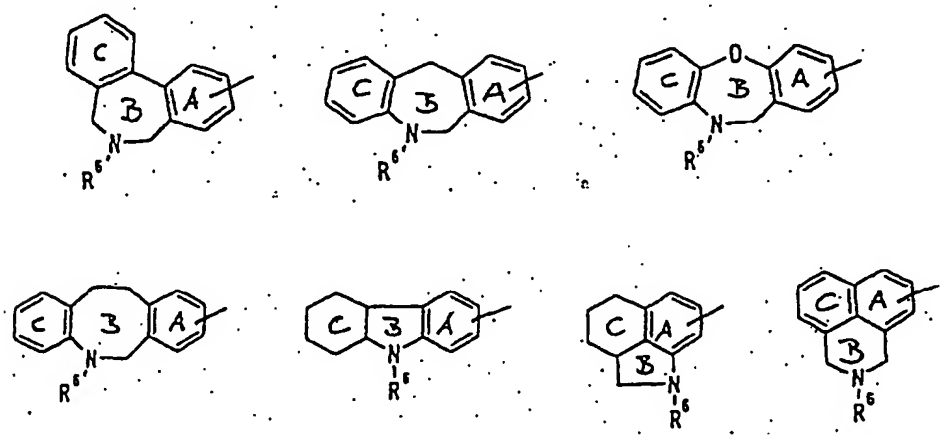
11. Zusammensetzung wie in Anspruch 10 beansprucht zur Verwendung bei der Behandlung von seniler Demenz und/oder Alzheimer-Krankheit.

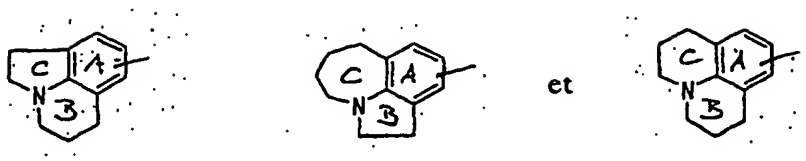
Revendications

1. Composé de formule

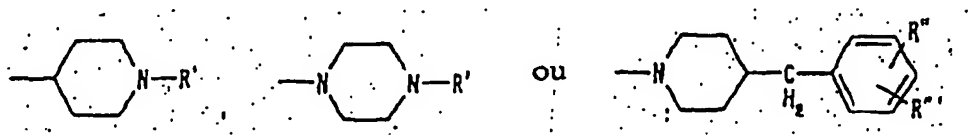
(I)

dans laquelle
Ar est choisi dans l'ensemble des groupes de formules :





dans lesquelles
le cycle A ne porte aucun substituant,
le cycle B ou C porte éventuellement un ou des substituants oxo et/ou alkyle en C_{1-6},
et R^6 représente un atome d'hydrogène ou un groupe alkyle en C_{1-6}, formyle, (alkyle en C_{1-6})carbonyle, benzoyle ou benzyle portant éventuellement un substituant alcoxy en C_{1-4};
Y représente un groupe de formule



dans laquelle
R' représente

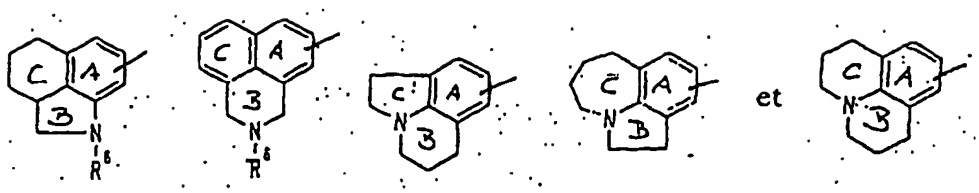
1) un groupe benzyle qui peut porter 1 ou 2 substituants choisis dans l'ensemble constitué par les atomes d'halogène et les groupes alkyle en C_{1-6}, nitro, cyano, amino, mono(alkyle en C_{1-6})amino, di(alkyle en C_{1-6}) amino, hydroxy, alcoxy en C_{1-6}, phényl-(alcoxy en C_{1-4}) et alkylènedioxy en C_{1-4},
2) un groupe cyclohexyle,
3) un groupe phényle,
4) un groupe formyle,
5) un groupe (alkyle en C_{1-6})carbonyle,
6) un groupe benzoyle,
7) un groupe (alcoxy en C_{1-6})carbonyle,
8) ou un atome d'hydrogène,

et R" et R"' sont identiques ou différents et représentent chacun un atome d'hydrogène ou d'halogène ou un groupe alkyle en C_{1-6}, nitro, cyano, hydroxy, alcoxy en C_{1-6}, phényl-(alcoxy en C_{1-4}) ou alkylènedioxy en C_{1-4} ;
et n représente le nombre entier 2 ou 3 ;
ou sel d'un tel composé.

2. Composé conforme à la revendication 1, dans lequel Y représente un groupe 4-pipéridinyle ou 1-pipérazinyle, qui porte éventuellement comme substituant

i) un groupe cyclohexyle,
ii) un groupe phényle,
iii) un groupe benzyle qui peut porter 1 ou 2 substituants choisis dans l'ensemble constitué par les atomes d'halogène et les groupes alkyle en C_{1-6}, alcoxy en C_{1-6}, hydroxy, nitro, amino et cyano,
iv) un groupe (alcoxy en C_{1-6})carbonyle,
v) un groupe (alkyle en C_{1-6})carbonyle,
vi) un groupe benzoyle,
vii) ou un groupe formyle.

3. Composé conforme à la revendication 1, dans lequel Ar est choisi dans l'ensemble des groupes de formules :



dans lesquelles les cycles A, B et C et le symbole R^6 ont les significations indiquées dans la revendication 1.

4. Composé conforme à la revendication 1, dans lequel Ar représente l'un des groupes suivants :

1,2,2a,3,4,5-hexahydrobenzo[cd]indol-6-yle,
1-formyl-1,2,2a,3,4,5-hexahydrobenzo[cd]indol-6-yle,
5,6-dihydro-2[1H]-oxo-4H-pyrrolo[3,2,1-ij]quinoléin-8-yle,
4-oxo-1,2,5,6-tétrahydro-4H-pyrrolo[3,2,1-ij]quinoléin-8-yle,
1,2,4,5,6,7-hexahydro-2-oxo-azépino[3,2,1-hi]indol-9-yle,
et 2,3,6,7-tétrahydro-5-oxo-1H,5H-benzo[ij]quinolizin-9-yle.

5. Composé conforme à la revendication 1, dans lequel Y représente un groupe 1-benzyl-4-pipéridinyle, 4-benzyl-1-pipérazinyle ou 4-benzyl-1-pipéridinyle.

6. Composé conforme à la revendication 1, qui est l'un des suivants :

- 8-(3-{4-[(3-méthylphényl)méthyl]-1-pipérazinyl}-1-oxopropyl)-1,2,5,6-tétrahydro-4H-pyrrolo[3,2,1-ij]quinoléin-4-one ou l'un de ses sels
- 8-(3-{4-[(3-chlorophényl)méthyl]-1-pipérazinyl}-1-oxopropyl)-1,2,5,6-tétrahydro-4H-pyrrolo[3,2,1-ij]quinoléin-4-one ou l'un de ses sels
- 8-(3-{4-[(2-méthylphényl)méthyl]-1-pipérazinyl}-1-oxopropyl)-5,6-dihydro-4H-pyrrolo[3,2,1-ij]quinoléin-2(1H)-4-one ou l'un de ses sels
- 8-(3-{4-[(3-chlorophényl)méthyl]-1-pipérazinyl}-1-oxopropyl)-5,6-dihydro-4H-pyrrolo[3 ,2,1-ij]quinoléin-2 (1H)-4-one ou l'un de ses sels
- 8-{3-[1-(phénylméthyl)-4-pipéridinyl]-1-oxopropyl}-1,2,5,6-tétrahydro-4H-pyrrolo[3,2,1-ij]quinoléin-4-one ou l'un de ses sels
- 8-(3-{1-[(4-méthylphényl)méthyl]-4-pipéridinyl}-1-oxopropyl)-1,2,5,6-tétrahydro-4H-pyrrolo[3,2,1-ij]quinoléin-4-one ou l'un de ses sels
- 8-(3-{1-[(3-méthoxyphényl)méthyl]-4-pipéridinyl}-1-oxopropyl)-1,2,5,6-tétrahydro-4H-pyrrolo[3,2,1-ij]quinoléin-4-one ou l'un de ses sels
- 8-(3-{1-[(2,4-diméthylphényl)méthyl]-4-pipéridinyl}-1-oxopropyl)-1,2,5,6-tétrahydro-4H-pyrrolo[3,2,1-ij]quinoléin-4-one ou l'un de ses sels
- 8-(3-{1-[(2,5-diméthylphényl)méthyl]-4-pipéridinyl}-1-oxopropyl)-1,2,5,6-tétrahydro-4H-pyrrolo[3,2,1-ij]quinoléin-4-one ou l'un de ses sels
- 8-(3-{1-[(4-chlorophényl)méthyl]-4-pipéridinyl}-1-oxopropyl)-1,2,5,6-tétrahydro-4H-pyrrolo[3,2,1-ij]quinoléin-4-one ou l'un de ses sels
- 8-(3-{1-[(4-nitrophényl)méthyl]-4-pipéridinyl}-1-oxopropyl)-1,2,5,6-tétrahydro-4H-pyrrolo[3,2,1-ij]quinoléin-4-one ou l'un de ses sels
- 8-(3-{1-[(phénylméthyl)méthyl]-4-pipéridinyl}-1-oxopropyl)-5,6-dihydro-4H-pyrrolo[3,2,1-ij]quinoléin-2(1H)-4-one ou l'un de ses sels
- 8-(3-{1-[(3-méthoxyphényl)méthyl]-4-pipéridinyl}-1-oxopropyl)-5,6-dihydro-4H-pyrrolo[3,2,1-ij]quinoléin-2 (1H)-4-one ou l'un de ses sels
- 8-{3-[4-(phénylméthyl)-1-pipéridinyl]-1-oxopropyl}-1,2,5,6-tétrahydro-4H-pyrrolo[3,2,1-ij]quinoléin-4-one ou l'un de ses sels
- 8-{3-[4-(phénylméthyl)-1-pipéridinyl]-1-oxopropyl}-5 ,6-dihydro-4H-pyrrolo[3,2,1-ij]quinoléin-2(1H)-4-one ou l'un de ses sels
- 1-(1,2,2a,3,4,5-hexahydrobenzo[cd]indol-6-yl)-3-[1-(phénylméthyl)pipéridin-4-yl]-1-propanone ou l'un de ses sels
- 1-(1-méthyl-1,2,2a,3,4,5-hexahydrobenzo[cd]indol-6-yl)-3-[1-(phénylméthyl)pipéridin-4-yl]-1-propanone ou l'un de ses sels

- 1-[2-(phénylméthyl)-2,3-dihydro-1H-benzo[de]isoquinoléin-6-yl]-3-[1-(phénylméthyl)-4-pipéridinyl]-1-propanone ou l'un de ses sels
- 8-(3-{1-[(3-fluorophényl)méthyl]-4-pipéridinyl}-1-oxopropyl)-1,2,5,6-tétrahydro-4H-pyrrolo[3,2,1-ij]quinoléin-4-one ou l'un de ses sels
- 8-(3-{1-[(2-hydroxyphényl)méthyl]-4-pipéridinyl}-1-oxopropyl)-1,2,5,6-tétrahydro-4H-pyrrolo[3,2,1-ij]quinoléin-4-one ou l'un de ses sels.

7. Procédé de préparation d'un composé conforme à la revendication 1, qui comporte

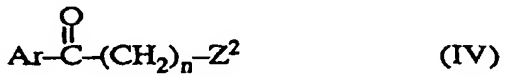
1) le fait de faire réagir un composé de formule

Ar-H (II)

dans laquelle Ar a la signification indiquée dans la revendication 1,
ou un sel d'un tel composé, avec un composé de formule

(III)

dans laquelle Z^1 représente un groupe partant et les autres symboles ont les significations indiquées dans la revendication 1,
ou avec un sel d'un tel composé ;
2) ou le fait de faire réagir un composé de formule



(IV)

ou un sel d'un tel composé, avec un composé de formule

Z^3-Y (V)

ou avec un sel d'un tel composé,
dans lesquelles formules Z^2 et Z^3 représentent des groupes qui peuvent s'éliminer en réagissant l'un avec l'autre, et les autres symboles ont les significations indiquées dans la revendication 1.

8. Composition pharmaceutique qui contient un composé conforme à la revendication 1.

9. Emploi d'un composé conforme à la revendication 1 ou d'un sel, admissible en pharmacie, d'un tel composé, dans la préparation d'une composition d'inhibiteur de cholinestérase.

10. Composition d'inhibiteur de cholinestérase, qui contient, en une quantité suffisante pour inhiber effectivement une cholinestérase, un composé conforme à la revendication 1 ou un sel, admissible en pharmacie, d'un tel composé, ainsi qu'un véhicule admissible en pharmacie.

11. Composition conforme à la revendication 10, destinée à être employée dans le traitement de la démence sénile et/ou de la maladie d'Alzheimer.